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Quinidine

Updated: May 10, 2018.

OVERVIEW

Introduction

Quinidine is a natural cinchona alkaloid which has potent antiarrhythmic activity and has been used for decades in the treatment of atrial and ventricular arrhythmias. Quinidine has been associated with fever, mild jaundice and clinically apparent liver injury in up to 2% of treated patients.

Background

Quinidine (kwin' i deen) and its stereoisomer quinine (kwye' nine) are natural cinchona alkaloids found in the powdered bark of the American cinchona tree. The bark powder was used for centuries in the prevention and therapy of malaria, but was also known to decrease heart palpitations. Quinidine was found to be the most potent of the antiarrhythmic substances extracted from the cinchona plant and was introduced into medical practice in the 1940s. Quinidine acts by depressing action potentials and is considered a myocardial depressant. It was formally approved for use in the United States in 1950 and was widely used to treat ventricular arrhythmias and to suppress the frequency of premature ventricular contractions. However, careful prospective studies demonstrated that suppression of ventricular arrhythmias can be associated with a decrease in survival and use of quinidine has fallen out of favor and now used largely for therapy of atrial flutter or fibrillation. Quinidine is also approved for intravenous use in treatment of life threatening Plasmodium falciparum malaria. Quinidine is available in multiple generic forms in tablets of 200 and 300 mg as well as in sustained release formulations and as a solution for intravenous administration. A typical maintenance dose of standard formulations in adults is 200 to 400 mg three to four times daily. Common side effects include dizziness, headache, tinnitus, blurred vision, gastrointestinal upset, diarrhea, nausea and skin rash.

Hepatotoxicity

Chronic therapy with quinidine is associated with a low rate of serum enzyme elevations, which are usually mild, asymptomatic and self limited even without alteration in dose. In addition, there have been many reports of acute hypersensitivity reactions to quinidine that include hepatic involvement. The reactions usually arise after 1 to 2 weeks of therapy, but can appear within 24 hours of restarting quinidine or with rechallenge. The clinical features are marked by fatigue, nausea, vomiting, diffuse muscle aches, arthralgias and high fever. Blood testing at an early stage shows increases in serum aminotransferase and alkaline phosphatase levels as well as mild jaundice, which can deepen for a few days even after stopping quinidine. The pattern of serum enzymes elevations is typically cholestatic or mixed. Rash is uncommon and eosinophilia is not typical, despite the presence of other signs of hypersensitivity (fever, arthralgias). Autoantibodies are not typically found. Liver biopsies usually show mild injury and small epithelioid granulomas, as are often found in many organs during

systemic hypersensitivity reactions. A similar clinical signature of liver injury occurs with quinine, an optical isomer of quinidine that is used predominantly as an antimalarial agent. In recent years, there have been few reports of liver injury attributed to quinidine, probably because it is now rarely used.

Likelihood score: A (well established cause of clinically apparent liver injury).

Mechanism of Injury

The hepatotoxicity of quinidine is clearly due to a hypersensitivity reaction and there is no evidence for a direct hepatotoxic effect of the drug. There is likely to be a genetic predisposition to this hypersensitivity.

Outcome and Management

The hepatotoxicity of quinidine is clearly a part of a hypersensitivity reaction and is usually mild, resolving within 1 to 4 weeks of stopping. In many instances, jaundice and liver test abnormalities may worsen for a few days after stopping, but fatalities have not been reported and recovery is usually rapid. Because of the rapidity of recovery, therapy with corticosteroids is usually best avoided. There is cross reactivity to quinine (the optical isomer of quinidine which is used as an antimalarial agent) and other exposures to quinidine should be avoided.

Drug Class: Antiarrhythmic Agents

See also: Quinine

CASE REPORT

Case 1. Acute hypersensitivity and cholestatic liver injury due to quinidine.

[Modified from: Koch MJ, Seeff LB, Crumley CE, Rabin L, Burns WA. Quinidine hepatitis: a report of a case and review of the literature. Gastroenterology 1976; 70: 1136-40. PubMed Citation]

A 47 year old man developed nausea, fever and right upper quadrant pain 10 days after starting quinidine for supraventricular tachycardias. He had a history of cardiac disease and was treated with furosemide, digoxin and nitroglycerin tablets chronically. He had no history of liver disease, alcohol abuse, risk factors for liver hepatitis or previous history of drug-allergies. Physical examination revealed a temperature of 101.6 ^{O}F, but normal white blood cell count and differential. Quinidine was continued and he continued to have fever. While serum bilirubin levels remained normal, ALT, AST and alkaline phosphatase levels were elevated starting a few days after the onset of fever (Table). Oral and intravenous cholangiograms were negative as were tests for hepatitis B. A liver biopsy was done which showed centrizonal hepatocellular necrosis and inflammation with prominent eosinophils suggestive of drug induced liver injury. Quinidine was stopped and the fevers and liver test abnormalities rapidly resolved. Because of recurrent arrhythmias despite use of procainamide, the patient was readmitted for a monitored rechallenge with quinidine. A day after taking four doses of quinidine (200 mg every 6 hours), he developed nausea and fever. Serum ALT levels rose from 18 to 52 U/L, while eosinophil counts, alkaline phosphatase levels and bilirubin values remained normal. Symptoms and ALT elevations resolved within two days.

Key Points

Medication:	Quinidine (200 mg every 6 hours)
Pattern:	Cholestatic-mixed-hepatocellular (R=1.4→12.0)
Severity:	1+ (symptoms and enzyme elevations without jaundice)
Latency:	10 days to symptoms

Table continued from previous page.

Recovery:	1-2 weeks
Other medications:	Digoxin, furosemide, nitroglycerin

Laboratory Values

Days After Starting	Days After Stopping	ALT* (U/L)	Alk P* (U/L)	Bilirubin* (mg/dL)	Other
Pre		26	81	0.4	Admission
10	0	40	90	Normal	Fever and nausea
14	0	110	225		
20	0	150	150		
24	0	370	100		Liver biopsy
30	0	680	190	Normal	Quinidine stopped
32	2	925	170		
36	6	345			
38	8	270	110		
Two months later rechallenged with quinidine 200 mg every 6 hours					
1	0	11			
2	1	18			
3	2	52	Normal	Normal	Fever and nausea
5	4	20			
Normal Values		**<40**	**<103**	**<1.2**	

* Some values estimated from Figure 1.

Comment

This patient developed signs of hypersensitivity to quinidine (fever) which resolved rapidly with stopping therapy. With continuation of the medication, liver test abnormalities arose that were initially cholestatic but eventually hepatocellular. The injury was mild in that there was no jaundice or hepatic synthetic dysfunction. Reexposure led to a more rapid onset of symptoms and liver test abnormalities, but they were still mild and rapidly reversible.

PRODUCT INFORMATION

REPRESENTATIVE TRADE NAMES

Quinidine – Generic

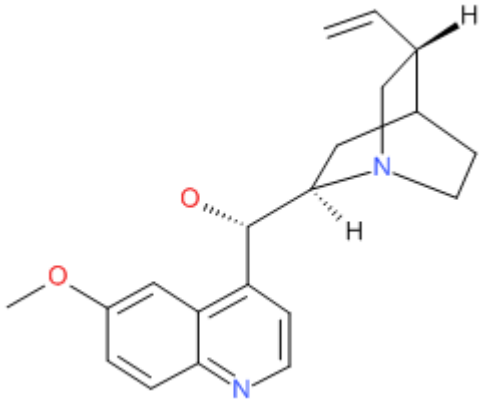
DRUG CLASS

Antiarrhythmic Agents

COMPLETE LABELING

Product labeling at DailyMed, National Library of Medicine, NIH

CHEMICAL FORMULA AND STRUCTURE

DRUG	CAS REGISTRY NUMBER	MOLECULAR FORMULA	STRUCTURE
Quinidine	56-54-2	C20-H24-N2-O2	

ANNOTATED BIBLIOGRAPHY

References updated: 10 May 2018

Zimmerman HJ. Antiarrhythmics. Drugs used in cardiovascular disease. In, Zimmerman HJ. Hepatotoxicity: the adverse effects of drugs and other chemicals on the liver. 2nd ed. Philadelphia: Lippincott, 1999, pp. 642-4.

(Expert review of hepatotoxicity of antiarrhythmics published in 1999; among the antiarrhythmics, only amiodarone and quinidine are common causes of hepatotoxicity; quinidine has been associated with many cases of clinically apparent, but mild liver injury usually with signs of hypersensitivity and hepatic granulomas).

De Marzio DH, Navarro VJ. Cardiovascular drugs. Hepatotoxicity of cardiovascular and antidiabetic drugs. In, Kaplowitz N, DeLeve LD, eds. Drug-induced liver disease. 3rd ed. Amsterdam: Elsevier, 2013, pp. 520-1.

(Review of hepatotoxicity of cardiovascular drugs including quinidine which appears to cause immunoallergic hepatitis arising within 1-2 weeks of starting).

Sampson KJ, Kass RS. Antiarrhythmic drugs. In, Brunton LL, Chabner BA, Knollman BC, eds. Goodman & Gilman's the pharmacological basis of therapeutics. 12th ed. New York: McGraw-Hill, 2011, pp. 815-48.

(Textbook of pharmacology and therapeutics).

Colding H. Et tilfaelde af kinidinallergi med feber og leverpavirkning. [A case of quinine-allergy with fever and liver injury]. Ugeskr Laeger 1969; 131: 1657-8. PubMed PMID: 5365434.

(74 year old woman developed fever and fatigue 2-3 weeks after starting quinine, with rise in bilirubin [0.4 to 2.0 mg/dL], AST [0.7 to 7.3 units] and Alk P [2.2 to 10.5 units] and resolution within 1 week of stopping; positive rechallenge).

Deisseroth A, Morganroth J, Winokour S. Quinidine-induced liver disease. Ann Intern Med 1972; 77: 595-7. PubMed PMID: 4642741.

(77 year old woman developed fever 11 days after starting quinidine followed by increases in ALT to ~210 U/L and LDH to 310 U/L, with prompt improvement upon stopping and recurrence of fever and ALT elevations within 24 hours of rechallenge).

Winkler JW. Quinidine hepatotoxicity? Ann Intern Med 1973; 78: 460. PubMed PMID: 4694908.

(Letter in response to Deisseroth et al. raising the issue of role of dioctyl calcium sulfosuccinate [Surfak] in the hepatic injury; authors reply that this was unlikely).

Murphy RJ, Rymer W. Quinidine induced liver disease? Ann Intern Med 1973; 78: 460. PubMed PMID: 4694908.

(62 year old man with 3 episodes of fever which in retrospect was thought to be due to quinidine with AST elevations of ~135 U/L, given challenge dose and developed fever to 39.4 but no change in AST).

Chajek T, Lehrer B, Geltner D, Levij IS. Quinidine-induced granulomatous hepatitis. Ann Intern Med 1974; 81: 774-6. PubMed PMID: 4433082.

(69 year old man developed fever 7 days after starting quinidine [bilirubin 1.0 mg/dL, Alk P 205 U/L, AST 430 U/L], resolving within a week of stopping; rechallenge led to fever within 24 hours and rise of AST to 250 U/L, Alk P 305 U/L, biopsy showing granulomas, repeat rechallenge showing the same with biopsy before and after).

Chajek T. Quinidine and granulomatous hepatitis. Ann Intern Med 1975; 82: 282. PubMed PMID: 1115455.

(After 1974 article, authors saw another case: 64 year old man developed fever 12 days after starting quinidine with Alk P and AST elevations and rapid improvement on stopping and recurrence on restarting, biopsy showing granulomas).

Handler SD, Hirsch NR, Hass K, Davidson FZ. Quinidine hepatitis. Arch Intern Med 1975; 135: 871-2. PubMed PMID: 48362.

(72 year old woman developed abnormal liver tests [AST 367 U/L] 7 months after starting quinidine, remaining elevated for 9 months and rising to AST 800 U/L [no jaundice and Alk P peak 110 U/L], rapid improvement with stopping and positive rechallenge to one dose with symptoms and AST rising to 110 U/L).

Koch MJ, Seeff LB, Crumley CE, Rabin L, Burns WA. Quinidine hepatitis: a report of a case and review of the literature. Gastroenterology 1976; 70: 1136-40. PubMed PMID: 1269875.

(47 year old man developed fever and abdominal pain 10 days after starting quinidine [normal bilirubin, ALT 910 U/L, Alk K 210 U/L], resolving rapidly when quinidine was stopped, and with recurrence of symptoms and mild ALT elevation within days of rechallenge: Case 1).

Geltner D, Chajek T, Rubinger D, Levij IS. Quinidine hypersensitivity and liver involvement: a survey of 32 patients. Gastroenterology 1976; 70: 650-2. PubMed PMID: 1261756.

(Among 487 patients who received quinidine over a 4 year period, 32 [6.5%] developed a hypersensitivity reaction, including 10 [2%] with liver involvement with fever, Alk P and AST elevations and jaundice in half usually after 4-14 days of therapy, resolving rapidly, liver biopsies showing granulomas and focal necrosis).

Dzur JR. Letter: Quinidine hepatotoxicity. JAMA 1976; 235: 908. PubMed PMID: 946110.

(Patient developed jaundice one month after starting quinidine, resolving with stopping; no details given).

Rotmensch HH, Rubinstein A, Livni E, Liron M, Ilie B. [Quinidine-induced subclinical hepatitis]. Harefuah. 1980; 98: 211-2. Hebrew. PubMed PMID: 6997146.

(68 year old man developed fever and arthralgias within weeks of starting quinidine, liver tests were normal but liver biopsy showed small granulomas and spotty hepatocyte necrosis; fever resolved within 7 days of stopping quinidine).

Bramlet DA, Posalaky Z, Olson R. Granulomatous hepatitis as a manifestation of quinidine hypersensitivity. Arch Intern Med 1980; 140: 395-7. PubMed PMID: 7362358.

(64 year old woman developed fever and fatigue one month after starting quinidine [bilirubin 1.8 mg/dL, ALT 327 U/L, Alk P 105 U/L], rapid resolution and positive rechallenge in one day with fever and AST elevation, underwent 3 liver biopsies showing presence, disappearance and reappearance of small granulomas).

Tiliakos N, Waites TF. Multiform quinidine toxicity. South Med J 1981; 74: 1267-8. PubMed PMID: 7197395.

(39 year old man developed fever, rash and fatigue 8 days after starting quinidine [4% eosinophils, thrombocytopenia, bilirubin 4 mg/dL, AST 280 U/L, Alk P 150 U/L], resolving rapidly upon stopping quinidine).

Slezak P. Quinidine hepatotoxicity. Med J Aust. 1981; 1: 139. PubMed PMID: 7219288.

(58 year old man developed fever, fatigue and abdominal pain 10 days after starting quinidine, followed by jaundice [bilirubin 1.6 mg/dL, ALT 208 U/L, Alk P 1.5 times ULN]).

Karoly R, Ferenc S. [An unusual side effect of quinidine: liver damage, pneumonia]. Orv Hetil 1983; 124: 055-6. Hungarian. PubMed PMID: 6634153.

(59 year old man developed fever, liver injury and pneumonitis within days of starting quinidine [bilirubin 3.1 mg/dL, ALT 120 U/L, Alk P 183 U/L, 6% eosinophils]).

Urdahl P, Bjørkheim A. [Quinidine-induced hepatitis. A case report and review of the literature]. Tidsskr Nor Laegeforen 1983; 103: 760-3. Norwegian. PubMed PMID: 6879565.

(60 year old woman developed fever and fatigue within a week of starting quinidine [bilirubin 2.7 mg/dL, ALT 292 U/L, Alk P 229 U/L], with rapid recovery and positive rechallenge).

Katz B, Weetch M, Chopra S. Quinine-induced granulomatous hepatitis. Br Med J 1983; 286: 264-5. PubMed PMID: 6402064.

(65 year old woman with episodic fever, nausea and polyarthralgias during 5 months of intermittent quinine use for leg cramps, [bilirubin 0.5 mg/dL, ALT 460 U/L, Alk P 375 U/L], biopsy showing granulomas; positive rechallenge with fever and ALT rising to 480 U/L).

Nirodi NS. Quinine induced granulomatous hepatitis. Br Med J (Clin Res Ed) 1983; 286: 647. PubMed PMID: 6402190.

(Letter questioning the presence of granulomas in case of Katz et al [1983]).

Smally AJ. When to leave well enough alone—two cases. Hosp Pract 1985; 20: 48-9. PubMed PMID: 3918052.

(Two cases of quinidine hepatotoxicity: 68 year old man with nausea and fever 10 days after starting quinidine followed by jaundice [bilirubin 5.4 mg/dL, AST 168 U/L, 3-4% eosinophils], and rapid recovery upon stopping; 54 year old man with onset of fever, fatigue and headache 3 weeks after starting quinidine [ALT 121 U/L], rapid resolution upon stopping).

Tanaka N, Matsushita E, Morimoto H, Kobayashi K, Hattori N. [Toxic hepatitis induced by cardiovascular agents]. Nippon Rinsho 1985; 43: 1172-5. Japanese. PubMed PMID: 3900470.

(Case series of drug induced liver disease due to cardiovascular agents, including one case due to quinidine).

Knobler H, Levij IS, Gavish D, Chajek-Shaul T. Quinidine-induced hepatitis: a common and reversible hypersensitivity reaction. Arch Intern Med 1986; 146: 526-8. PubMed PMID: 3954525.

(Among 90 cases of drug induced liver injury seen over 10 years in one referral hospital, 33 were due to quinidine [2% of recipients] with typical signature of fever, arising within first 4 weeks of therapy, both Alk P and ALT modestly elevated, only 6 with jaundice, none fulminant, all resolved rapidly with no long term consequences; 8 rechallenged and all redeveloped fever, 6 had Alk P and AST elevations as well).

Zatuchni J. Quinidine-induced hepatitis. Arch Intern Med 1986; 146: 2077, 2081. PubMed PMID: 3767557.

(Letter questioning Knobler et al [1986] why quinidine was used so much in view of its questionable efficacy; reply by authors).

Pariente EA, Maitre F, Marchand JP. [Hepatitis caused by quinidine. Study of a case and review of the literature]. Gastroenterol Clin Biol 1986; 10: 255-8. French. PubMed PMID: 3732735.

(63 year old woman developed fatigue and jaundice 1 month after starting quinidine [bilirubin 2.2 mg/dL, ALT 109 U/L, Alk P 684 U/L], biopsy showing granulomas, rapid recovery, but she had persistent hepatomegaly and elevated Alk P in follow up).

Bourlière M, Bernuau J, Rueff B, Benhamou JP. Quinidine phenylethyl-barbiturate-induced fulminant hepatitis in a pregnant woman. A case report. J Hepatol 1988; 6: 214-6. PubMed PMID: 3411101.

(19 year old pregnant woman developed rash and fever one month after starting quinidine and barbiturate [bilirubin 1.6 rising to 18.8 mg/dL, ALT 296 to 800 U/L, Alk P 267 U/L, prothrombin index 13%], delivering normal baby, but subsequently developing hepatic failure and undergoing successful liver transplant).

Alix M, Mosquet B, Adrien A, Cuny G, Raffy P, Moulin M. [Cholestatic hepatitis caused by quinidine phenylethylbarbiturate, and sarcoidosis. Apropos of a case]. Therapie 1989; 44: 69. French. PubMed PMID: 2734725.

(68 year old woman developed jaundice 2 months after starting quinidine and a barbiturate with mild fever [bilirubin 15 mg/dL, ALT 200 U/L, Alk P 342 U/L], improved with stopping, but enzymes remained high and follow up liver biopsy suggested sarcoidosis).

Mathur S, Dooley J, Scheuer PJ. Quinine induced granulomatous hepatitis and vasculitis. BMJ 1990; 300: 613. PubMed PMID: 2108777.

(67 year old man developed fever, rash and polyarthralgias 2 months after starting intermittent quinine therapy for leg cramps [bilirubin 0.6 mg/dL, AST 100 U/L, Alk P 1668 U/L], granulomas on biopsy and rapid recovery upon stopping).

Punukollu RC, Kumar S, Mullen KD. Quinine hepatotoxicity: an underrecognized or rare phenomenon? Arch Intern Med 1990; 150: 1112-3. PubMed PMID: 2331190.

(37 year old woman developed fever, arthralgias and abdominal pain without rash 2-3 weeks after starting quinine for leg cramps [bilirubin 1.8 mg/dL, ALT 128 U/L, Alk P 327 U/L, eosinophils 6%], resolving within 1 week of stopping quinine, and subsequent positive rechallenge to one dose with fever and ALT rising to 64 U/L).

Perez JA, Stryker J, Arsura EL, Hewitt JM. Probable quinine-induced hepatotoxicity. West J Med 1994; 160: 59-60 PubMed PMID: 8128710.

(74 year old man developed fever, abdominal pain and jaundice one month after starting quinine for leg cramps [bilirubin 7.2 mg/dL, ALT 241 U/L, Alk P 314 U/L, ESR 65], biopsy showing granulomas and rapid resolution upon stopping).

Man-Song-Hing M, Wells G. Meta-analysis of efficacy of quinine for treatment of nocturnal leg cramps in elderly people. BMJ 1995; 10: 13-7. PubMed PMID: 7827545.

(Meta analysis of 107 patients from 6 clinical trials; quinine reduced number of nights with leg cramps by 27%).

Horney E, Lagerstedt C, Wadenvik H. [A case report. Thrombocytopenia and granulomatous hepatitis caused by quinine]. Lakartidningen 1996; 93: 361-4. Swedish. PubMed PMID: 8628066.

(58 year old man developed intermittent fevers with ALT 185 U/L, GGT 145 U/L, normal bilirubin, but thrombocytopenia; positive rechallenge).

Hou M, Horney E, Stockelberg D, Jacobsson S, Kutti J, Wadenvik H. Multiple quinine-dependent antibodies in a patient with episodic thrombocytopenia, neutropenia, lymphocytopenia, and granulomatous hepatitis. Blood 1997; 90: 4806-11. PubMed PMID: 9389697.

(58 year old man with recurrent, transient bouts of fever, nausea, thrombocytopenia and ALT elevations [4-6 times ULN] shown to be due to intermittent exposure to quinine, with positive rechallenge and demonstration of quinine dependent antibodies to platelets and white blood cells).

Farver DK, Lavin MN. Quinine-induced hepatotoxicity. Ann Pharmacother 1999: 33: 32-4. PubMed PMID: 9972382.

(57 year old woman developed fever, nausea and myalgias within 24 hours of starting quinine for leg cramps with temperature 39.5 ^{o}C [bilirubin 0.7 mg/dL, ALT 184 U/L, Alk P 192 U/L], resolving within 3 weeks of stopping).

Howard MA, Hibbard AB, Terrell DR, Medina PJ, Vesely SK, George JN. Quinine allergy causing acute severe systemic illness: report of 4 patients manifesting multiple hematologic, renal, and hepatic abnormalities. Proc (Bayl Univ Med Cent) 2003; 16: 21-6. PubMed PMID: 16278718.

(Four women developed quinine induced thrombocytopenia with other systemic manifestations, including prominent AST [131, 992, 741 and 3735 U/L] and mild Alk P [74-170 U/L] elevations and 2 with jaundice [bilirubin 4.3 and 16.1 mg/dL], often due to inadvertent quinine use from over-the-counter pills).

Schlegel A. Factitious granulomatous hepatitis? Am J Med 2004; 116: 500-1. PubMed PMID: 15047046.

(35 year old woman with relapsing episodes of fever, abdominal pain and ALT elevations [1488 U/L] and biopsy showing small granulomas who finally confessed to intermittent, purposeful use of quinine).

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

(Review of toxicities and safety of antimalarials: quinine can cause a characteristic hypersensitivity reaction with liver injury).

Drugs for cardiac arrhythmias. Treat Guidel Med Lett 2007; 5: 51-8. PubMed PMID: 17505408.

(Concise review of drugs for arrhythmias; quinidine is rarely used mainly because of toxicity and poor tolerability, currently used as an alternative therapy for suppression of supraventricular tachycardia and atrial fibrillation; mentions granulomatous hepatitis as an adverse event).

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, neither quinine nor quinidine is mentioned).

Reuben A, Koch DG, Lee WM; Acute Liver Failure Study Group. Drug-induced acute liver failure: results of a U.S. multicenter, prospective study. Hepatology 2010; 52: 2065-76. PubMed PMID: 20949552.

(Among 1198 patients with acute liver failure enrolled in a US prospective study between 1998 and 2007, 133 were attributed to drug induced liver injury, none of which were attributed to quinidine or quinine).

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. PubMed PMID: 23419359.

(In a population based study of drug induced liver injury from Iceland, 96 cases were identified over a 2 year period, but none were attributed to quinidine or quinine).

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.

(Systematic review of literature of drug induced liver injury in Latin American countries published from 1996 to 2012 identified 176 cases, none of which were attributed to quinidine or quinine).

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.e7. 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 quinine or quinidine).