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Antiarrhythmic Agents

Updated: July 6, 2017.

OVERVIEW

The antiarrhythmics are a heterogeneous group of medications that act to decrease cardiac automaticity and slow conduction, and are used for either or both ventricular and atrial arrhythmias. The most common use of antiarrhythmics is in the treatment of atrial fibrillation or flutter, or prevention of their recurrence in patients after electrical or medical cardioversion. Use of antiarrhythmics for suppression of ventricular arrhythmias is controversial in that several studies have shown that suppression of ventricular premature contractions can be associated with a decrease rather than increase in survival. Thus, the antiarrhythmics are generally used only for clinically significant ventricular dysrrhythmias.

The oral antiarrhythmics are often separated into classes based upon their major molecular target as either class I (sodium channel), II (beta adrenergic receptor), III (potassium channel), or IV (calcium channel). Many agents have multiple targets, but the classification is helpful particularly because of shared side effects.

Oral antiarrhythmics available in the United States (and their year of approval) include quinidine (1950), procainamide (1950), disopyramide (1977), amiodarone (1985), flecainide (1985), mexiletine (1985), propafenone (1989) and dronedarone (2009). Agents used intravenously, usually for a short period only with severe arrhythmias, include adenosine (1989), ibutilide (1995), isoproterenol (1992) and dofetilide (2000). Agents used to slow atrial-ventricular conduction include cardiac glycosides (digoxin, digitoxin), calcium channel blockers (diltiazem, verapamil), and beta adrenergic blockers (esmolol, propranolol, and sotalol) which are discussed elsewhere.

Amiodarone is a well established cause of drug induced liver injury and can cause both an acute as well as a chronic liver injury with cirrhosis. Dronedarone, a non-iodinated derivative of amiodarone, has been implicated in several cases of severe acute liver failure and may share the propensity for hepatotoxicity of amiodarone. The other antiarrhythmics are rare causes of liver injury, their cardiac and central nervous system adverse events usually overshadowing the idiosyncratic effects on the liver. General references are provided after this introduction and specific references on hepatotoxicity are given after the description of each of the following agents:

- Amiodarone
- Disopyramide
- Dofetilide
- Dronedarone
- Flecainide
- Ivabradine
- Mexiletine
- Procainamide

- Propafenone
- Quinidine

ANNOTATED BIBLIOGRAPHY

References updated: 06 July 2017

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 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; disopyramide has been linked to at least 10 cases of drug induced liver disease, mexiletine to 6 cases, and propafenone and flecainide to rare cases of cholestatic jaundice).

De Maurzio DH, Navarro VJ. Hepatotoxicity of cardiovascular and antidiabetic drugs. In, Kaplowitz N, DeLeve LD, eds. Drug-induced liver disease. 3rd ed. Amsterdam: Elsevier, 2013, pp. 519-40.

(Review of hepatotoxicity of antiarrhythmics with specific discussion of amiodarone, dronedarone, procainamide, quinidine, and propafenone).

Sampson KJ, Kass RS. Anti-arrhythmic 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).

Koch-Weser J. Disopyramide. N Engl J Med 1979; 300: 957-62. PubMed PMID: 431563.

(Review of disopyramide; mechanism of action is unclear, myocardial depressant and has anticholinergic activity which accounts for side effects of urinary retention, visual blurring, constipation and nausea. Acute psychoses, cholestatic jaundice, hypoglycemia and agranulocytosis have occurred in rare patients).

Scheinman SJ, Poll DS, Wolfson S. Acute cardiac failure and hepatic ischemia induced by disopyramide phosphate. Yale J Biol Med 1980; 53: 361-6. PubMed PMID: 7222741.

(2 patients developed heart failure and raised serum enzymes within 1-2 days of starting disopyramide [AST rising to 4780 and 1495 U/L, bilirubin peak 2.1 mg/dL, Alk P normal], resolving within 7-8 days).

Arif M, Laidlaw JC, Oshrain C, Willis PW 3rd, Nissen CH, McDermott DJ, Smith WS, et al. A randomized, double-blind, parallel group comparison of disopyramide phosphate and quinidine in patients with cardiac arrhythmias. Angiology 1983; 34: 393-400. PubMed PMID: 6408949.

(124 patients with ventricular arrhythmias received disopyramide or quinidine for 8 weeks; AST elevations occurred in 3 on quinidine and 1 on disopyramide but none had symptoms or jaundice).

Libersa C, Caron J, Pladys A, Beuscart R, Kacet S, Wajman A, Connell C, et al. Propafenone versus disopyramide: a double-blind randomized crossover trial in patients presenting chronic ventricular arrhythmias. Clin Cardiol 1987; 10: 405-10. PubMed PMID: 2440632.

(Ten patients with ventricular arrhythmias were treated with disopyramide vs propafenone vs placebo in a crossover study for 6 days each; no change in chemical parameters).

Propafenone for cardiac arrhythmias. Med Lett Drugs Ther 1990; 32: 37-8. PubMed PMID: 2182990.

(Short summary of efficacy and safety of propafenone published soon after its approval in the US; adverse effects include dizziness, change in taste, blurred vision, abdominal discomfort, anorexia, and nausea; can worsen heart failure; no mention of hepatic adverse effects).

Flecainide for supraventricular tachyarrhythmias. Med Lett Drugs Ther 1992; 34: 71-2. PubMed PMID: 1630411.

(Short summary of efficacy and safety of flecainide published soon after its approval in the US; adverse effects include dizziness and blurred vision, but recommended restricted use because of its proarrhythmic effects).

Echt DS, Liebson PR, Mitchell LB, Peters RW, Obias-Manno D, Barker AH, Arensberg D, et al. Mortality and morbidity in patients receiving encainide, flecainide, or placebo. The Cardiac Arrhythmia Suppression Trial. N Engl J Med 1991; 324: 781-8. PubMed PMID: 1900101.

(Among 1498 patients with myocardial infarction and ventricular ectopy, 323 were treated with flecainide and 318 to placebo and followed for a mean of 10 months; there was an excess mortality from cardiac arrest in antiarrhythmic treated patients; no mention of hepatotoxicity or ALT elevations).

Roden DM. Antiarrhythmic drugs: from mechanisms to clinical practice. Heart 2000; 84: 339-46. PubMed PMID: 10956304.

(Overview of antiarrhythmic drugs which are separated in four classes based upon molecular target: I being sodium channel blockers; II beta blockers; III potassium channel blockers, and IV calcium channel blockers; some agents having multiple targets).

McNamara RL, Tamariz LJ, Segal JB, Bass EB. Management of atrial fibrillation: review of the evidence for the role of pharmacologic therapy, electrical cardioversion, and echocardiography. Ann Intern Med 2003; 139: 1018-33. PubMed PMID: 14678922.

(Systematic review of literature on efficacy and safety of medications for atrial fibrillation; no discussion of hepatic side effects).

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

(Concise review of drugs for arrhythmias).

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 from 2004 to 2008, 2 cases were attributed to amiodarone and 1 to propafenone, but none to other antiarrhythmics such as quinidine, procainamide, disopyramide, flecainide, or mexiletine).

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 an antiarrhythmic agent).

Treatment of atrial fibrillation. Treat Guidel Med Lett 2010; 8 (97): 65-70; PubMed PMID: 20733547.

(Concise review of efficacy and safety of drugs for atrial fibrillation including amiodarone, disopyramide, dofetilide, dronedarone, flecainide, propafenone, and sotalol; only amiodarone, dronedarone and propafenone are listed as having adverse effects of hepatotoxicity).

Safety of dronedarone (Multaq). Med Lett Drugs Ther 2011; 53 (1379-1380): 103-4. PubMed PMID: 22173456.

(Concise review of adverse effects of dronedarone, which include hepatotoxicity and an increased risk of death from cardiovascular causes).

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, one of which was due to amiodarone, but in no other case was an antiarrhythmic agent implicated).

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, 2 of which were attributed to propafenone, but none to amiodarone or dronedarone).

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, 7 were attributed to antiarrhythmic agents including 5 due to amiodarone and 2 to dronedarone).