AMIODARONE (Systemic)

Commonly used brand name(s):Cordarone; Cordarone I.V.; Cordarone Intravenous.

Category

Antiarrhythmic.

Indications

Accepted

Arrhythmias, ventricular (prophylaxis and treatment)¾Amiodarone in the oral dosage form is indicated only for the treatment of recurrent hemodynamically unstable ventricular tachycardia and recurrent ventricular fibrillation unresponsive to documented adequate doses of other available antiarrhythmic medications or when alternative agents cannot be tolerated 1.

In patients for whom the oral form of amiodarone is indicated, but who are unable to take oral medication, the intravenous form of amiodarone may be used 35.

Mechanism of action/Effect:

Amiodarone prolongs the action potential duration 1, 3, 4, 9, 10, 14, 94 and the refractory period 1, 3, 4, 8, 9, 14, 69 in all cardiac tissues (including the sinus node, atrium, atrioventricular [AV] node, and ventricle) 3, 4, 7, 8, 9, 23 by a direct action on the tissues 3, 4 , without significantly affecting the membrane potential 1, 9, 14.

Amiodarone also decreases sinus node automaticity 4, 7, 8, 9, 23 and junctional automaticity 99 , prolongs AV conduction 3, 7, 8, 9, 23 , and slows automaticity of spontaneously firing fibers in the Purkinje system 4, 9.

Refractoriness is prolonged and conduction is slowed in accessory pathway tissue in patients with Wolff-Parkinson-White (W-P-W) syndrome 8, 9, 34, 42, 44.

Noncompetitive alpha- and beta-adrenergic receptor antagonism and calcium channel inhibition also occur 1, 2, 3, 4, 8, 9, 10, 14, 92 and thyroid hormone metabolism is affected 1, 3, 4, 8, 9, 19, 24, 50, 56, 85 , but the relationship of these effects to the antiarrhythmic action of amiodarone is unknown. In the Vaughan Williams classification of antiarrhythmics, amiodarone is considered to be a predominantly class III agent 127 , with some class I properties.

Precautions to Consider

Carcinogenicity/Tumorigenicity

Studies in rats at doses one-half the maximum recommended human maintenance dose and greater found a dose-related increase in the incidence of thyroid follicular adenomas and/or carcinomas 1, 78.

Mutagenicity

Mutagenicity studies (Ames, micronucleus, and lysogenic tests) with amiodarone were negative [1, 78].

Pregnancy/Reproduction

Fertility¾Studies in male and female rats at doses eight times the maximum recommended human maintenance dose found that amiodarone reduced fertility [1, 78].

Pregnancy¾Amiodarone crosses the placenta [8, 9, 43, 110]; neonatal plasma concentrations of amiodarone and desethylamiodarone are 10% [43, 110] and 25% [29, 110] of maternal plasma concentrations, respectively. Although studies in humans have not been done, some reports have indicated an absence of adverse effects when amiodarone was administered late in pregnancy [43, 110].

However, amiodarone can cause fetal harm when administered to pregnant women. 78 Potential adverse effects include bradycardia [9, 29] and effects on thyroid status [8, 9, 29, 110] (iodine is known to cause fetal goiter, hypothyroidism, and mental retardation [110]) in the neonate. There have been a small number of reports of congenital goiter/hypothyroidism and hyperthyroidism. 78

Studies in rats and one strain of mice at doses 18 times and one half the maximum recommended human maintenance dose, respectively, have shown that amiodarone is embryotoxic. 78 Amiodarone was not embryotoxic in a second strain of mice or in rabbits at doses up to nine times the maximum recommended human maintenance dose. 1

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Labor and delivery¾Although studies in humans have not been done, studies in rodents found no adverse effects of amiodarone on duration of gestation or on parturition [1].

Breast-feeding

Amiodarone is distributed into human breast milk. [1, 29, 78] The infant receives approximately 25% of the maternal dose [9, 29].

Amiodarone has been shown to cause reduced viability and growth of offspring when used in lactating rats. Mothers should be advised to contact physician before nursing, since use by nursing mothers is not recommended [1, 29, 78].

Pediatrics

99.

Drug interactions and/or related problems

The following drug interactions and/or related problems have been selected on the basis of their potential clinical significance (possible mechanism in parentheses where appropriate)¾not necessarily inclusive (>> = major clinical significance):

Note: Because of its slow elimination, amiodarone may interact with other medications for weeks to months after it is discontinued. 52

Combinations containing any of the following medications, depending on the amount present, may also interact with this medication.

Anesthetics, inhalation

(amiodarone may potentiate hypotension and atropine-resistant bradycardia 3, 6, 7, 9)

>> Antiarrhythmics, other

(amiodarone may produce additive cardiac effects with other antiarrhythmics and increase the risk of tachyarrhythmias 1 ; amiodarone increases plasma concentrations of quinidine, procainamide, flecainide, and phenytoin 1, 7, 8, 9, 108 ; concurrent use of amiodarone with quinidine, disopyramide, procainamide, or mexiletine has been reported to result in a more prolonged QT interval and, rarely 127 , torsades de pointes , 7, 8, 9, 12 and therefore, concurrent use with all class I antiarrhythmics requires great caution 3, 8 ; the doses of previously given antiarrhythmics should be reduced by 30 to 50% several days after initiation of amiodarone therapy and gradually withdrawn 1, 8, 9 ; if antiarrhythmic therapy is needed in addition to amiodarone, it should be initiated at one half the usual recommended dose 1, 7)

>> Anticoagulants, coumarin-derivative

(amiodarone inhibits metabolism 105 and potentiates the anticoagulant effect 1, 3, 7, 8, 9, 12, 24, 84, 86, 108, 119 , beginning as early as 4 to 6 days after initiation of amiodarone therapy 8, 9, 84 and persisting as long as weeks or months after it is withdrawn 9, 119 ; prothrombin times may double or triple 8 , but effect is very erratic 127 ; it is recommended that the dose of anticoagulant be reduced by one third to one half and that prothrombin times be monitored closely 1, 7, 8, 9, 24, 84, 119)

Beta-adrenergic blocking agents or

Calcium channel blocking agents

(amiodarone may cause potentiation of bradycardia, sinus arrest, and atrioventricular [AV] block 1, 7, 8, 23, 85 , especially in patients with underlying sinus function impairment 7, 85.

If this occurs, dosage reduction of amiodarone or the beta-blocking agent or calcium channel blocking agent is recommended 99 ; in some cases, amiodarone therapy may be continued after insertion of a pacemaker 1)

>> Digitalis glycosides

(amiodarone increases serum concentrations of digoxin and probably other digitalis glycosides 1, 3, 7, 8, 9, 12, 13, 79, 85, 107, 108, 111, 112 , possibly to toxic levels; when amiodarone therapy is initiated, the digitalis glycoside should be withdrawn or the dose reduced by 50% 1, 7, 8, 9, 79 ; if digitalis glycoside therapy is continued, serum concentrations should be carefully monitored 1, 8, 24,

79, 107 ; amiodarone and digitalis glycosides may also produce additive effects on sinoatrial [SA] and AV nodes 9)

Diuretics, loop or

Diuretics, thiazide or

Indapamide

(concurrent use of amiodarone with potassium-depleting diuretics may lead to an increased risk of arrhythmias associated with hypokalemia 127)

>> Phenytoin

(amiodarone may increase plasma concentrations of phenytoin, resulting in increased effects and/or toxicity 1, 36, 58, 91)