Amiadarone hydrochloride (cordarone)

CAS: 19774-82-4
MF: $C_{25}H_{29}I_2NO_3$ • HCl (amiodarone hydrochloride)
MW: 681.8
Solubility: very slightly soluble in water. For injection each ml contains 50 mg of amiodarone hydrochloride, 20.2 mg benzyl alcohol, 100 mg polysorbate 80, and water.

Major use
Amiodarone is a cardiac drug for treatment of life threatening supraventricular and ventricular arrhythmias refractory to other drugs. It was initially developed over 20 years ago for the treatment of angina pectoris.

Human toxicity
Acute toxicity of amiodarone is relatively low; it is slightly toxic at the higher doses.

Therapeutic doses in adults may be up to 5 mg/kg (maximum 20 mg/kg) or 2 g/day. Adults ingesting 2.6 to 8 g developed asymptomatic slight bradycardia (a slow heartbeat) and hypotension. Nausea, vomiting, constipation, and anorexia occur frequently with ingestion of grater than 1 g of amiodarone at a single dose. In substantial overdose, bradycardia and/or heart block, torsades de pointes, and hypotension should be anticipated. The most severe adverse effect is pulmonary fibrosis, which has 10% mortality rate.

Therapeutic blood concentration is in the range of 0.75-2.5 mg/l. Steady-state amiodarone concentrations of 1 to 2.5 mg/l have been associated with antiarrhythmic effects and acceptable toxicity following chronic oral administration therapy.

Amiadarone is considered to give adverse reactions at the serum concentrations exceeding 2.5-3.0 mg/l (reviewed in [1]).

Kinetic data
Absorption: Amiodarone is absorbed slowly. It is extremely lipid soluble and accumulates in high concentrations in most tissues, particularly in adipose tissue, lungs and liver. The concentration in the myocardium may be 10 to 50 times higher that in plasma. Oral bioavailability is ranged from 22 to 86%.

Volume of distribution: about 60 l/kg.

Plasma peak concentration is reached after 3-7 h (after oral ingestion), and after 1-24 h after intravenous administration.

Therapeutic effect may take from 2 to 21 days to occur.

Protein binding: up to 96%.

The serum half-life for amiodarone is 35-68 days, and for its metabolite desethylamiodarone it is 31-110 days.

Elimination half-life can take from 8 to 107 days (20 to 47 days according Daily Med, via Internet). The elimination of amiodarone from plasma after withdrawal is biphasic [2].

Metabolism and excretion
Amiodarone is an iodinated benzofuran derivative, structurally related to the thyroid hormone thyroxine. Amiodarone is metabolized predominantly by the liver [1]. Two known metabolites are desethylamiodarone and di-desethylamiodarone. Desethylamiodarone has also antiarrhythmic activity; it is rapidly accumulated in the lung after amiodarone treatment, sometimes at higher concentrations than amiodarone itself. It proved to be more toxic than amiodarone in pulmonary cell types; may play an important role in amiodarone-induced pulmonary fibrosis [2, 3].

Excretion: About 1% is excreted unchanged to the urine. The main routes of elimination are via hepatic excretion and via gall-bladder into bile.

Toxicological mechanisms
Amiodarone depresses heart sinus node function and prolongs the PR, QRS and QT intervals (the intervals are routinely scanned by ECG) [1]. Amiadarone inhibits the function of the β-adrenergic system and therefore it is a noncompetitive α- and β-antagonist [2].

Target organs: cardiovascular system, lung, liver.

References
[1] Poisindex, Thomson Micromedex (2005).
[2] Mason, J.W. (1987) Amiadarone. New Engl J Med, 316 (8), 455-465.
[3] Nacarelli, G.V., Rinkenberger, R.L., Dougherty, A.H., Fitzgerald, D.M. (1989) Adverse effects of amiodarone: Pathogenesis, incidence and management. Med Toxicol Adverse Drug Exp 4(4), 246-253.

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