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Distribution of Amiodarone and Desethylamiodarone in a Patient with Acute Myocardial Infarction After Intravenous Administration

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Summary: The autopsy tissues concentration of amiodarone and desethylamiodarone of a man with acute myocardial infarction treated acutely with intravenous amiodarone is reported. Our data indicate that amiodarone is quickly distributed into all highly perfused tissues after intravenous administration with a high amiodarone/desethylamiodarone ratio. We also report here the autopsy case of a woman who died after 30 days of oral therapy with amiodarone. The increase in heart/plasma ratio of amiodarone and desethylamiodarone concentrations and the decrease in amiodarone/desethylamiodarone ratio after one month of therapy could explain the latency in the antiarrhythmic action of the drug.

Key words: amiodarone, desethylamiodarone, tissue distribution, myocardial infarction

Introduction

Amiodarone is a well known antiarrhythmic agent effective on supraventricular and ventricular arrhythmias. Its metabolite, desethylamiodarone, has been proved to have a similar electrophysiologic profile[1] and, for this reason, could contribute to the amiodarone antiarrhythmic properties.

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Amiodarone and desethylamiodarone (DE-Amiodarone) distribution has been studied in patients during short- and long-term treatment through biopsy[2,3] and autopsy samples.[3,4] The atrial and myocardial uptake has been evaluated within 24 hours after oral administration.[2] No data are available on the acute (24 hours) distribution of the drug into cardiac and extracardiac tissues in patients with acute myocardial infarction. We report here the autopsy case of a man with myocardial infarction treated acutely with intravenous amiodarone. We also report the autopsy case of a woman who died after 30 days of oral therapy with amiodarone.

Case Report 1

LB, a 62-year-old man weighing 45 kg had essential hypertension and right hemiplegia. On 7/4/84 he was admitted to the hospital with the diagnosis of acute myocardial infarction complicated by pulmonary edema. He was treated with digitalis, diuretics, and morphine. On 7/5/84 his creatine phosphokinase (CPK) was 610 U (normal range <100 U). At 6 P.M. he developed a new episode of pulmonary edema and was treated with digoxin, diuretics, and nitroglycerin. At 8:30 P.M. he developed supraventricular tachyarrhythmia and was given amiodarone (300 mg in 100 cc NaCl 0.9%) intravenously over 30-min. On 7/6/84 his CPK was 930 U. At 10 A.M. he received amiodarone (300 mg in 100 cc NaCl 0.9%) intravenously over 30-min. At 12 P.M. his CPK was 1110 U. At 5 P.M. he became increasingly dyspneic, hypotensive, and diaphoretic with systemic vasoconstriction. He expired at 5:30 P.M. Twenty minutes after his death a blood sample was taken. On 7/9/84 an autopsy was performed which showed a recent subendocardial myocardial infarction involving the entire wall of the left ventricle, a moderate amount of left ventricular hypertrophy, and cardiomegaly. Several tissue samples were taken.

Case Report 2

AB was a 57-year-old female weighing 46 kg who had a history of ischemic heart disease and apical aneurysm of the left ventricle. On 2/7/84 she was started on amiodarone regimen for frequent ventricular ectopy. Initially she was given amiodarone 200 mg per orally t.i.d. for two days. The dose was decreased on 2/9/84 to 200 mg b.i.d. and to 200 mg q.d. on 2/22/84. The last dose was given on 3/8/84 at 8 A.M. The patient expired on 3/9/84 at 8 P.M. during cardiac surgery for coronary revascularization and aneurysmectomy. During the operation, a blood sample was taken. The total dose of amiodarone was 9.6 g. Tissue samples were taken during autopsy on 3/12/84.

In both patients, tissue and plasma samples were assayed for amiodarone and DE-amiodarone by high pressure liquid chromatography.[5] These values are reported in Table I.

Discussion

Amiodarone, a highly lipophilic drug, is largely distributed in most tissues.[6] Experimental studies in dogs have shown that the drug reaches peak myocardial concentration 20 minutes after intravenous administration.[5] The time course of electrophysiologic effect correlated with myocardial concentration better than with plasma.[7] In humans, peak myocardial concentration of amiodarone and DE-amiodarone has been reported to be reached within 24 hours after administration of a single oral dose (30 mg/kg).[2] Since the oral bioavailability of amiodarone is about 35–65%,[8,9] the total dose of 13 mg/kg intravenously taken by patient LB can be compared to the oral dose of 30 mg/kg. In this patient, the plasma concentration of amiodarone and DE-amiodarone and the myocardial concentration of amiodarone are of the same order of magnitude of a previous study[2] while the myocardial concentration of DE-amiodarone is greater. In patient LB the high tissue/plasma ratio of amiodarone shows the rapid distribution of the drug in the highly perfused tissues. The amiodarone/DE-amiodarone ratio is >5 in all the highly perfused tissues except in the liver where it is 2. Tissue/plasma ratios of amiodarone and DE-amiodarone concentrations in patient AB, chronically treated for 1 month, were much higher than in patient LB, who received a single intravenous bolus; this is somewhat in agreement with a previous report from our group.[4] DE-amiodarone showed a higher tissue/plasma ratio than amiodarone in both cases but tended to accumulate less than the parent compound in fat. The amiodarone/DE-amiodarone ratio was always greater than 2 in patient LB, while it was lower

TABLE I Amiodarone and desethylamiodarone distribution

	A (μg/g)	DEA (μg/g)	A/DEA	At / Ap	DEAt / DEAp
Patient LB					
Plasma	2.00 μg/ml	0.9 μg/ml	22.2	—	—
Brain	NM	NM	—	—	
Fat	17.31	4.74	3.66	8.65	52.67
Kidney	16.61	2.82	5.89	8.30	31.33
Liver	66.07	32.71	2.02	33.03	363.4
Lung	191.95	31.78	6.04	95.9	353.11
Thyroid	10.62	1.74	6.10	5.31	19.33
Ventricle	28.13	5.22	5.39	14.06	58.0
Red blood cells	0.62	0.12	5.17	0.31	1.33
Skeletal muscle	2.98	NM	—	1.49	—
Patient AB					
Plasma	0.52 μg/ml	0.32 μg/ml	1.62	—	—
Brain	2.8	19.9	0.14	5.4	62.2
Fat	142.1	28.7	4.95	273.2	89.7
Kidney	7.2	33.7	0.21	13.8	105.3
Liver	64.7	331.9	0.19	124.4	1037.2
Lung	149.8	623.0	0.24	288.1	1946.9
Thyroid	7.8	16.0	0.49	15.0	50.0
Ventricle	12.0	51.6	0.23	23.1	161.3
Atrium	18.3	20.5	0.89	35.2	64.1
Spleen	3.7	40.1	0.09	7.1	125.3
Skin	122.0	27.7	4.40	234.6	86.6

Abbreviations: A=amiodarone; DEA=desethylamiodarone; NM=not measurable (<0.05 μg/g); p=plasma; t=tissue.

than 1 in all tissues except plasma, fat, and skin in patient AB. So, the DE-amiodarone contribution to the electrophysiologic action of amiodarone increases during chronic treatment.[1]

Some conclusions can be drawn, keeping in mind two major limitations of our study. First, only two cases were studied; second, total concentration of a drug in tissues represents not only the active part, bound to receptors or available at the site of action, but also a large amount nonspecifically bound to the tissue which does not directly contribute to drug action. Our data indicate that amiodarone is quickly distributed into all highly perfused tissues after intravenous administration in a patient with acute myocardial infarction. Some DE-amiodarone is produced during the first 24 hours and distributes to tissues although with a high amiodarone/DE-amiodarone tissue ratio. The increase in heart/plasma ratio of amiodarone and DE-amiodarone concentrations and the decrease in amiodarone/DE-amiodarone ratio during chronic treatment are two factors to be considered when trying to explain the latency, often observed in the antiarrhythmic action of the drug. A threshold concentration of the metabolite or an optimal ratio amiodarone/DE-amiodarone could be required for the efficacy.

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