Title: AMRINONE INHIBITS INTRACORONARY THROMBUS FORMATION AND PROTECTS AGAINST MYOCARDIAL ISCHEMIA IN DOGS

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Introduction. The probable cause of myocardial infarction and perhaps unstable angina in human beings is believed to be acute rupture or fissuring of an atherosclerotic plaque, followed by intracoronary thrombosis. The most important event linking plaque rupture and thrombosis is platelet activation and aggregation. This harmful process may be accelerated by endogenous substances such as thromboxane and epinephrine. Drugs that stabilize platelets can protect against myocardial infarction. Recently much interest has been generated by aspirin. Epinephrine is an inotrope and potent platelet activator that stimulates acute arterial thrombus formation and in vitro platelet aggregation even after pretreatment with aspirin. Amrinone, a useful inotrope and vasodilator is quite unlike typical antiplatelet drugs, however, it may inhibit phosphodiesterase and in this way stabilize platelet function. Our aim was to determine whether or not amrinone would inhibit intracoronary thrombus formation, improve coronary blood flow, and protect against ischemia.

Methods. A dog model designed to resemble important aspects of human coronary stenosis--critical stenosis in conjunction with endothelial damage--was used.[1] Five dogs were anesthetized and their chests opened. A critical stenosis was induced with a circumferential plastic constrictor around the circumflex coronary artery and at this site the vascular endothelium was damaged by briefly squeezing the artery with forceps. Platelet thrombosis and dislodgement occurred, producing cyclical reductions in circumflex blood flow. Flow reductions were measured using an electromagnetic flow probe. Myocardial ischemia resulting from cyclical reductions in blood flow was assessed using subendocardial ventricular wall sonomicrometry, intraventricular measurement of dp/dt and by epicardial ECG monitoring. For 30 minutes, spontaneous reductions in blood flow were assessed. Next, epinephrine, a known stimulator of platelet aggregation was infused intravenously (0.25 µg/kg/min) and observations continued. The experiment was repeated following amrinone administered incrementally (4 mg/kg) and by constant intravenous infusion (20 µg/kg/min).

Results. Cyclical reductions in coronary blood flow produced by platelet thrombosis occurred spontaneously in 4 of 5 dogs and were associated with severe myocardial ischemia. Epinephrine infusion induced frequent and severe reductions in blood flow with ischemia in all 5 dogs. Amrinone completely abolished spontaneous cyclical reductions in coronary blood flow and prevented myocardial ischemia in all animals. Preliminary data suggest amrinone also abolishes thrombus formation induced by epinephrine. Figure 1 shows typical cyclical reductions in coronary blood flow and the accompanying deterioration in ventricular function. Amrinone administration resulted in prompt abolition of thrombus induced coronary blood flow reductions. Coronary blood flow and ventricular function are preserved.

Discussion. In dogs, amrinone protects against myocardial ischemia caused by intracoronary platelet thrombosis. Amrinone is not only an inotrope, but in addition, has a potent antithrombotic effect. The mechanism of action is unknown but may involve inhibition of platelet phosphodiesterase or platelet thromboxane synthetase.[2] We speculate that if amrinone were to have similar effects in human beings with coronary artery disease and post-coronary bypass surgery, it may be unique in both stimulating the heart and simultaneously protecting against coronary thrombosis.

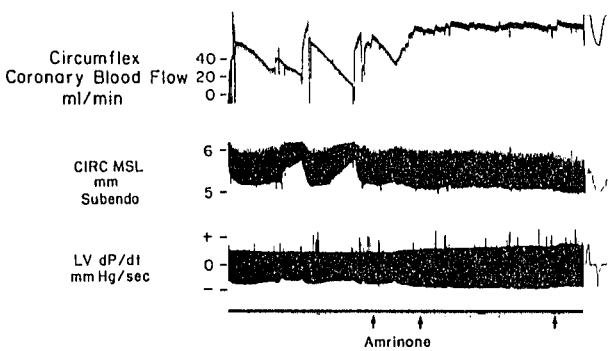

Fig. 1: Amrinone, 2 cc or 0.4 mg/kg, administered at first arrow resulted in abolition of thrombus induced flow reduction with total 4 mg/kg dose given by final arrow.

References.

1. Folts JD, Crowell EB, Rowe GG: Platelet aggregation in partially obstructed vessels and their elimination with aspirin. Circulation 54:365-370, 1976
2. Lippton HL, Horwitz PM, McNamara DB, et al: The effects of amrinone on human platelet aggregation: evidence that amrinone does not act through a cyclic nucleotide mechanism in platelet rich plasma. Prostaglandins Leukotrienes Med 18:193-204, 1985