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INTRAVENOUS AMIODARONE IN ACUTE ANTERIOR MYOCARDIAL INFARCTION: A CONTROLLED STUDY

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SUMMARY. A randomized, single-blind controlled study intended to assess the potential benefits of intravenous amiodarone in anterior myocardial infarction is presented. Three hundred nineteen patients entered the study, 159 received amiodarone infusion, and 160 received glucose-insulin-potassium (GIK) infusion. Basal characteristics were similar in the two experimental groups, who were randomized on a consecutive basis. Exclusion criteria were shock or pulmonary edema, hypotension, inferoposterior infarction, bradycardia, antrioventricular block, severe diabetes, and other major diseases.

Patients aged 27 to 70 years, with a Q-wave anterior infarction, initiated 12-40 hours earlier at the time of admission, entered the trial. Other entry criteria were heart rate higher than 80 beats/min and systolic blood pressure higher than 100 mmHg. Amiodarone was administered in saline infusion 10-20 mg/kg, within 4 to 10 hours, through a central vein. GIK infusion consisted of 150-300 g of glucose, 25-50 IU of insulin, and 80-120 mEq of KCl in 1000 cc of water at a rate of 1.5-2.0 ml/g/hour. Both groups received digitalis, nitrates, sedatives, and diuretics as needed.

Although individually the major endpoints of death, reinfarction, and sustained supraventricular and ventricular arrhythmias did not differ significantly, each was less in the amiodarone group than in the control, and the sum of all adverse events was significantly lower for the amiodarone patients ($p < 001$). Heart failure and conduction disturbances were not different in the two groups.

This study shows that amiodarone, with its vasodilating and antiarrhythmic properties, may be beneficial in acute anterior infarction, but further studies on larger populations will be necessary in order to show a reduction of mortality rate.

KEY WORDS. amiodarone, anterior myocardial infarction, antiarrhythmic agent

Amiodarone, a potent class III antiarrhythmic agent, possesses vasodilating and antianginal properties [1]. It exerts several actions that may benefit the ischemic myocardium: Due to vasodilating effects and noncompetitive beta-blocking properties, it reduces afterload and heart rate, and reduces contractility, which—in the setting of ischemic heart disease—may be beneficial when balanced by afterload reduction [2-4]. The result of these combined effects is a decrease of myocardial oxygen demand and this, associated with potent antiarrhythmic action, may be valuable for the treatment of acute myocardial ischemia.

De Boaer et al. have shown decreased infarct size in dogs after experimental ligation of coronary artery and treatment with amiodarone [5]. Coté et al. have shown favorable effects on cardiac and coronary hemodynamics and on myocardial metabolism in patients with coronary disease and ischemia at rest [4]. Lotto et al. found a significant reduction of heart rate in acute myocardial infarction linearly related to baseline heart rate, but they also noted an increase in pulmonary wedge pressure and a reduction of cardiac index in a group of patients who had contraindications to beta-blocking drugs [3]. This observation was at variance with the finding of Coté et al., who reported a rather stable or slightly increased cardiac output due to a reduction of systemic vascular resistance that outbalanced the slight dose-dependent inotropic negative action of amiodarone [4]. Other work [6] proved that reduction of systemic vascular resistance is independent of the solvent (Tween 80), as previously suggested by Lotto et al.

On these grounds, we began this work in order to study the potential clinical benefit of amiodarone in patients with acute myocardial infarction. For this purpose, we selected the acute anterior transmural infarction, which is most often associated with sympathetic overactivity, and excluded infarction of the inferoposterior wall, which is usually associated with increased parasympathetic activity, sinus bradycardia, and/or antrioventricular block [7].

As a control group, we selected patients with comparable clinical conditions treated with our standard therapy, consisting of glucose-insulin-potassium (GIK) infusion for all patients with no contraindication to such a regimen. This form of treatment, first started by Sodi-Pallares, was validated by Rogers et al., who have shown reduction of arrhythmias, of infarct size, and of hospital mortality [8, 9] with this regimen.

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Methods

Three hundred nineteen patients, aged 27 to 70 years, with an anterior (Q-wave) myocardial infarction initiated 12-40 hours before the time of admission to our coronary care unit, entered the trial. Other entry criteria were heart rate higher than 80 beats/min and systolic blood pressure higher than 100 mmHg. Patients hospitalized within 12 hours after the onset of symptoms were excluded because they entered the GISSI trial with intravenous streptokinase [10]. Exclusion criteria were inferior or posterior infarction, shock or pulmonary edema on admission, hypotension, atrioventricular conduction defects, bradycardia, severe diabetes requiring insulin, and other major diseases. Intraventricular conduction defects without atrioventricular disturbances were not considered among exclusion criteria. Randomization was achieved on a consecutive basis, and treatment was not blinded since true blinding would have been very difficult, if not impossible, using intravenous amiodarone versus GIK infusion. Amiodarone was administered as following: 10-20 mg/g of body weight in saline infusion, the first 150 mg of which were injected within 20 minutes and the remaining dose within 4–10 hours, depending on heart rate, pressure, rhythm, and clinical hemodynamic variations. Once the heart rate was reduced to 80 or lower, the infusion was stopped. Otherwise, an oral maintenance dose of 600 mg/day was started. A central vein was preferred for infusion of both amiodarone and GIK infusion, since phlebitis is not an uncommon complication when a scalp vein is used, and a necrotizing process may take place if these fluids leak out of a vein into the surrounding tissue.

In the GIK group, 150-300 g of glucose, 25-50 IU of insulin and 80-120 mEq of potassium chloride in 1000 cc of water were infused at a rate of 1.5-2.0 ml/Kg/hour. The infusion was continued up to 3 or 5 days, and adjustments of concentration of glucose, insulin, and potassium were made on the basis of serum values. All patients were treated in a coronary care unit and subsequently in the post-intensive ward until discharge.

Both groups received nitrates, digitalis, diuretics, and sedatives as needed. In the control group, lidocaine was used for ventricular arrhythmias, and in cases of refractoriness the patient crossed over to amiodarone infusion. In the amiodarone group, when sustained or recurrent ventricular arrhythmias developed, the rate of infusion was increased or a new infusion was started if the previous one was over. In cases of resistance, the patient crossed over to lidocaine or GIK infusion, to which 3 g of magnesium sulphate per 500 cc were added. Beta-blockers were used almost exclusively in the control group when needed.

Table 1 illustrated the baseline characteristics of the two groups of patients in the trial, and Table 2 shows the drugs administered after randomization.

Analysis of Results

All events reported here are hospital events occurring from the day of admission to the coronary care unit to discharge from the cardiology ward. The principal endpoint was vascular death; other events considered for analysis were early reinfarction, ventricular or supraventricular sustained arrhythmias, cardiac arrest, heart failure, recurring angina, atrioventricular block, new intraventricular conduction defects, emboli, need for pacemaker implantation, and left ventricular thrombosis at two-dimensional echocardiography. Subsidiary analysis was made on some combined endpoints. Figures were based on intention to treat according to initial randomization, and the significance of differences observed was evaluated by the Chi square test.

Table 1. Baseline characteristics of patients at entry

Entry Data	Amiodarone (n = I59)	Controls (n = I60)	p
Age (years)	54 ± 9	55 ± 3	ns
Female	I5(9.4)	I3(8.I)	ns
Previous infarction	22(I3.8)	I8(II.2)	ns
Diabetes	I4(8.8)	I2(7.5)	ns
Hypertension	26(I6.3)	I8(II.2)	ns
Mean heart rate	I02 ± I0	I00 ± 8	ns
Systolic pressure	I20 ± I3	I20 ± 6	ns
Bundle branch block	II(6.9)	8(5)	ns
Mean delay for admission (hrs)	22.6 ± 9	2I.4 ± 7	ns

Percentages in brackets.

Table 2. Drugs used after randomization

Drug	Amiodarone	Control	p
Amiodarone	159(100)	8(5)	
GIK	4(2.5)	160(100)	
Nitrates	48(30.1)	55(34.3)	ns
Beta-blockers	4(2.5)	84(52.5)	<.001
Analgesia or sedation	78(49)	84(52.5)	ns
Digitalis and or diuretics	20(12.5)	25(15.6)	ns
Antiarrhythmics	6(3.7)	29(18.1)	<.01
Anticoagulant or fibrinolitis	18(11.3)	24(15.0)	ns
Other inotropics	6(3.7)	11(6.8)	ns

GIK = glucose-insulin-potassium
Percentages in brackets

Definitions

Sustained ventricular tachycardia: a ventricular tachycardia lasting 30 seconds or more.

Sustained atrial arrhythmia: a supraventricular arrhythmia lasting over a minute or requiring treatment.

Early arrhythmias: arrhythmias occurring within 48 hours of admission.

Late arrhythmias: arrhythmias occurring later than 48 hours after admission.

Results

The two groups were comparable as regards for baseline characteristics and number. The length of hospitalization and stay in the coronary care was not different in the two groups. Table 3 summarizes the principal events observed in the two groups: No single event was statistically different, but the sum of total endpoints was significantly lower in the amiodarone group ($p < .001$).

A left ventricular aneurysm was diagnosed using two-dimensional echo in 18.2% and in 20% of the amiodarone and the GIK groups, respectively (NS). Thirteen (8.1%) and 11 (6.8%) thrombi were observed in the former and in latter groups (NS), respectively. Heart failure, AV block, emboli, and the need for early surgery were evenly distributed in both groups. Digitalis and diuretics were used equally, whereas beta-blockers and antiarrhythmic drugs were employed significantly more in the GIK group. Subsidiary analysis of combined events that may affect mortality is shown in Table 4. Death, reinfarction, and sustained arrhythmias had a considerably lower incidence in the amiodarone group ($p < .001$), and early and late arrhythmias were also significantly lower in this group ($p < .01$).

Amiodarone had to be prematurely interruped in three patients due to hemodynamic deterioration (increasing rales on the lung fields, pulmonary edema, or profound hypotension), and these patients were managed with digitalis and diuretics or other inotropic drugs. Other side effects included headache (6.9%), flushing (5.6%), slight hypotension (4.4%), and bradycardia (6.9%). These did not require treatment and subsided for the most part, by reducing the infusion rate. The GIK infusion was prematurely interrupted in four patients who developed pulmonary edema, in four patients with hypoglycemia, and in eight patients with resistant arrhythmias who crossed over to amiodarone. In most patients on amiodarone, typical signs on the electrocardiogram developed, but a very long QT interval with pronounced U wave was observed in only four patients with low potassium levels, who were treated with the addition of GIK and magnesium infusion for recurrent and refactory ventricular arrhythmias.

No significant difference was observed in the type of death in the two groups as to whether it was arrhythmic or was due to heart failure.

Table 3. Results of amiodarone trial in acute anterior MI

Endpoint	Amiodarone Group ($n = 159$)	Control Group ($n = 160$)	p
Death	17 (10.3)	21 (13.1)	ns
Infarct extension	14 (8.8)	19 (11.8)	ns
Early VT or F	7 (4.4)	13 (8.1)	ns
Late VT or F	3 (1.8)	8 (5)	ns
Atrial f or F	2 (1.2)	7 (4.3)	ns
Cardiac arrest	4 (2.5)	4 (2.5)	ns
Angina	22 (13.8)	29 (18.1)	ns
Heart failure	14 (8.8)	12 (7.5)	ns
AVB	6 (3.7)	4 (2.5)	ns
IVCD	10 (6.2)	11 (6.8)	ns
Emboli	4 (2.5)	8 (5)	ns
Pacemaker	2 (1.2)	2 (1.2)	ns
Early surgery	4 (2.5)	7 (4.3)	ns
TOTAL	113	145	<.001

Percentages in brackets.
VT = ventricular tachycardia; F = fibrillation; f = flutter; AVB = atrioventricular block; IVCD = intraventricular conduction defects

Table 4. Subsidiary analysis on combined major events

Events	Amiodarone (159)	Controls (160)	X2	p
Death + reinfarction + arrhythmias	57(35.8)	80(50)	31.02	<.001
Atrial and ventricular arrhythmias (sustained)	26(16.3)	40(25)	5.96	<.01

Discussion

Despite the limitation of population size, the results of this study seem to support the suggestion that intravenous amiodarone is beneficial in acute anterior myocardial infarction. The principal endpoint, death rate, was 10.3% in the experimental group and 13.1% in the control group. This difference is not statistically significant, but it might reach significance in a larger

population. Arrhythmias, both ventricular and supraventricular, were significantly lower in the amiodarone group. Similarly, combined events such as death, reinfarction, and arrhythmias at subsidiary analysis were also significantly lower in the amiodarone group.

The incidence of heart failure was almost identical in the two groups, thus excluding a pronounced negative inotropic effect for amiodarone. Nevertheless, the rate of infusion requires careful surveillance and frequently needs to be slowed in patients with large infarcts and in Killip class II. The theoretical advantage of amiodarone over beta-blockers is the lowering effect on systemic resistances, which are left unchanged or may even increase with beta-blockers.

Another point worth mentioning is that among patients with intraventricular conduction defects at entry, only one patient presented antrioventricular block needing a temporary pacemaker in the amiodarone group and none presented in the GIK group. Intraventricular conduction defects developed in 6.2% and 6.8% of the amiodarone and the control groups, respectively, and in all such instances amiodarone and beta-blockers (when in therapy) were reduced or suspended. But mortality was high in both groups, as expected in such a setting that carriers a high risk of death and heart failure. Permanent pacemaker, embolization, septal or chordal rupture, or any need for early surgery were equal in the two groups.

This study is the first clinical trial with a controlled design on amiodarone in myocardial infarction administered by intravenous route in a rather early phase of infarction. Our results are at variance with the work of Hockings et al. [11], who observed no benefit, despite reduction of arrhythmias, in patients with acute infarction treated with 600 mg of amiodarone by mouth and followed up to 9 months. It is obvious that amiodarone injected by vein has a more rapid effect, and its lowering action on peripheral resistance may be lost when administered per os. Moreover, a brief period of therapy, as in our trial, should render most of the well-known side effects of amiodarone most unlikely to occur (thyroid, lungs, eyes). In conclusion, this preliminary study seems to justify a larger trial on the possible benefits of amiodarone in acute myocardial infarction, possibly as an alternative to beta-blockers.

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