CARDIAC AND PULMONARY REPLACEMENT

ELECTROPHYSIOLOGIC EFFECTS OF PROCAINAMIDE, MEXILETINE, AND AMIODARONE ON THE TRANSPLANTED HEART

Experimental study

The effects of procainamide, mexiletine, and amiodarone on automaticity, conduction, and refractoriness were studied in a model of heterotopic heart transplantation in dogs that combined an innervated heart (recipient) and a denervated transplanted heart (donor). After the surgical procedure, 500 mg procainamide ($n = 13$), 200 mg plus 0.1 mg/kg per minute mexiletine ($n = 10$), or 150 mg amiodarone ($n = 10$) was administered intravenously. During a baseline period and after drug administration, each heart was assessed for atrioventricular interval; cycle length; sinoatrial conduction time; atrioventricular node antegrade and retrograde block points; atrioventricular node and ventricular antegrade effective refractory periods; PR, QRS, and QT intervals on electrocardiogram; systemic arterial, pulmonary arterial, central venous, and pulmonary capillary wedge pressures; and cardiac output. In recipients, procainamide reduced cardiac output, depressed sinus automaticity, slowed conduction time without affecting the QRS interval, and prolonged the nodal and ventricular refractoriness; in donor hearts, it depressed automaticity and prolonged nodal refractoriness, but did not modify conduction or ventricular refractoriness. Mexiletine only moderately depressed sinus automaticity in recipient hearts; it did not affect the other parameters either in recipient or transplanted hearts, nor did it alter the hemodynamic situation. Amiodarone produced hypotension, reduced cardiac output, and prolonged all the electrophysiologic intervals except the QRS interval in recipient hearts. These changes were even more pronounced in the transplanted hearts and led to extreme sinus bradycardia in four cases. Of these three drugs, mexiletine appears to be the safest should treatment for arrhythmias be necessary in transplant recipients. (*J THORAC CARDIOVASC SURG* 1995;109:899-904)

L. Alvarez, PhD, FCCP,^a C. Escudero, PhD,^a A. Torralba, PhD,^b and I. Millán, MS,^c Madrid, Spain

Accelerated coronary artery disease is a complication that occurs systematically after heart transplantation, constituting the third most frequent cause of death. At Stanford, it has been reported to be the determinant of 60% of retransplantation procedures.¹ The patients do not normally report angina because the heart is denervated, and the first

signs of the development of this complication are usually life-threatening ventricular arrhythmias, congestive heart failure as a result of myocardial ischemia, silent myocardial infarction, and sudden death.

There is not a great deal of information concerning the response of the transplanted heart to different drugs^{2,3} or, more specifically, to antiarrhythmic agents. The purpose of this report was to compare the action of procainamide (class IA), mexiletine (class IB), and amiodarone (class III) on the conduction system of transplanted hearts with the effects of these agents on normal hearts, with use of a model of heterotopic transplantation in dogs.

These drugs were selected because procainamide and amiodarone are administered intravenously with certain frequency, the former to assess the

From the Experimental Surgery Service,^a Hospital Pharmacy,^b and Biostatistics Service,^c Clínica Puerta de Hierro, Madrid, Spain.

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Address for reprints: Lourdes Alvarez, PhD, FCCP, Rafael Bergamín, 9, 28043 Madrid, Spain.

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response of an arrhythmia to long-term oral treatment and the latter for short-term control of certain severe ventricular arrhythmias.⁴ Although amiodarone is classified as a class III agent among the antiarrhythmic drugs,⁵ it also exhibits class IB action⁶; thus it was considered appropriate to include mexiletine in the study.

Material and methods

Heart transplantation was done in healthy, adult mongrel dogs that weighed between 20 and 25 kg; the weights of the donor dogs ranged from 15 to 20 kg. Care of the animals complied with the rules stipulated by the "Principles of Laboratory Animal Care" and the "Guide for the Care and Use of Laboratory Animals" issued by the National Society for Medical Research and the National Academy of Sciences, respectively.

The animals were divided into three groups according to the drug they received: procainamide ($n = 13$), 500 mg bolus over 5 minutes, resulting in a dosage range of 20 to 25 mg/kg body weight; mexiletine ($n = 10$), 200 mg bolus over 5 minutes, followed by continuous infusion of 0.1 mg/kg per minute; or amiodarone ($n = 11$), 150 mg bolus over 2 minutes, resulting in a dosage range of 7 to 7.5 mg/kg body weight.

Anesthesia was induced with thiopental (20 mg/kg body weight). After endotracheal intubation, the dogs were connected to an Ohmeda 7000 ventilator (Ohmeda, BOC, Madison, Wis.) and the lungs ventilated at a tidal volume of 15 to 20 ml/kg body weight. Maintenance of anesthesia was achieved with diazepam (a single 5 mg dose after intubation), fentanyl (5 to 10 μ g/kg body weight), pancuronium bromide (2 mg after intubation and 1 mg/hour), and 30% oxygen and nitrous oxide. No additional drugs were administered in the 90 minutes before the electrophysiologic studies were done; thus, once thoracotomy was concluded, anesthesia was maintained exclusively with oxygen and nitrous oxide. Oxygenation and acid-base status were monitored both in transplanted and recipient hearts throughout the trial, as were systemic arterial pressure and surface electrocardiogram.

In the recipients, in addition to electrocardiogram and determination of arterial pressure, central venous pressure, pulmonary arterial pressure, pulmonary capillary wedge pressure, and cardiac output were measured during a baseline period, after transplantation, and between 5 and 15 minutes after infusion of the antiarrhythmic agent by introducing a 7F Swan-Ganz catheter (Baxter Healthcare Corp., Edwards Div., Santa Ana, Calif.) into the right external jugular vein. Central venous pressure was maintained constant throughout the procedure by means of fluid infusion.

The surgical technique used for transplantation was that described by Barbero-Marcial and associates,⁷ in which the left chambers of the two hearts are connected in parallel, without extracorporeal circulation. To this end, the left atria and the aortas of donor and recipient were anastomosed. Because in this transplant model the right cavities of the donor were deprived of systemic connection, the pulmonary artery was anastomosed to the left

atrial appendage to create a passageway into the bloodstream of the coronary sinus: although this established a right-to-left shunt, it had no hemodynamic or oxymetric impact.

The transplanted heart was subjected to a period of ischemia of approximately 45 to 50 minutes. Satisfactory recovery of the heartbeat occurred spontaneously or was achieved by means of electric shock, and sinus rhythm was reestablished immediately in all cases.

Once the hemodynamic situation stabilized and normothermia was achieved in the transplanted myocardium, fixed pentapolar reference electrodes were sutured into the epicardium of the right chambers of the two hearts. The electrodes were connected to a computer-assisted system based on microprocessors that was capable of integrating the signals, listing the results on a display, printing them, and plotting them on previously designed maps.⁸

The signals thus obtained were filtered between 50 and 500 Hz. With these signals, and by means of the system's internal stimulator,⁹ programmed stimulation of the two hearts was achieved (5 V of amplitude and 1 msec of pulse width). The electrogram printout was obtained by interconnecting the system to an HTR-8 polygraph (PPG Hellige GmbH, Freiburg, Germany).

The electrophysiologic study included the following determinations.

Cycle length. The cycle length (CL) measures the interval of time between two spontaneous cardiac cycles and thus is the inverse of the heart rate, as expressed by the equation $CL = 6 \times 10^4 \cdot \text{heart rate}^{-1}$. It is used to assess sinus node automaticity.

Sinoatrial conduction time. The sinoatrial conduction time (SACT) reflects the capacity of transmission of an impulse originating in the sinus node to the perisinus area. This was determined by the method described by Narula and associates,¹⁰ which consists of atrial stimulation by a train of eight stimuli at a rate slightly higher than the spontaneous rate. The SACT is the difference between the first poststimulation cycle and the basic spontaneous cycle, divided by 2.

Antegrade block point and retrograde block point. The antegrade block point (ABP) and retrograde block point of the atrioventricular node were defined as the longest (atrial or ventricular) CL at which Wenckebach periodicity occurred during incremental (atrial or ventricular) pacing. They were calculated by stimulation of atrium and ventricle, respectively, at CLs that decreased progressively by 50 msec. These parameters assess the capacity of the atrioventricular node to conduct stimuli antegradely and retrogradely and thus are a measure, although indirect and somewhat imprecise, of the nodal refractoriness.

Effective refractory periods. The antegrade effective refractory period of the atrioventricular node (ARPAVN) and the ventricular effective refractory period (VRP) were defined as the longest interval of time between two stimuli, the basic stimulus and the extrastimulus, in which the latter did not achieve a propagated response. They were calculated by stimulation, atrial and ventricular, respectively, at a fixed cycle and introduction of an extrastimulus with progressive reduction by 8 msec of the coupling interval. These parameters are used to assess the

Table I. Hemodynamic study

	sAP	dAP	CVP	sPA	dPA	WP	CO
Basal	162.5 ± 27.5	92.1 ± 17.9	2.1 ± 1.2	14 ± 3.4	8.2 ± 2.5	4.7 ± 2.1	3.8 ± 1.2
Tx	149 ± 27	87.7 ± 16.4	3.8 ± 1.9	14.4 ± 3.9	12.3 ± 5.5	10 ± 2.4	3.3 ± 0.9
After P	154.2 ± 30.1	92.4 ± 15	3.6 ± 2.1	16.3 ± 3.8	12.7 ± 1.9	8.8 ± 1.6	3 ± 1*
Basal	177.1 ± 24.8	113.6 ± 12.2	4.6 ± 2.6	21.1 ± 4.9	14 ± 4	10.6 ± 4.4	5.8 ± 2.1
Tx	171.5 ± 22.3	101.9 ± 15.7	4.1 ± 2	21.1 ± 7.1	15.7 ± 5.4	8.6 ± 3.2	5.5 ± 2.1
After M	165.5 ± 22	102.5 ± 13	4.2 ± 1.8	22 ± 8.5	15.6 ± 3.7	7.9 ± 3	4.7 ± 2
Basal	168.1 ± 22.9	99 ± 25.8	4.1 ± 1.6	15.8 ± 2.3	9.9 ± 2.8	6.3 ± 3.2	3.4 ± 1.6
Tx	151.7 ± 28.4	90.1 ± 18.5	3.7 ± 2.1	17.2 ± 6.7	9.7 ± 5.6	6.1 ± 2.4	2.4 ± 1
After A	86.9 ± 32.6*	49.3 ± 18*	2.1 ± 1.2†	16.4 ± 4.4	8.3 ± 5.4	4.2 ± 2.3	1.6 ± 0.5†

sAP, Systolic arterial pressure; dAP, diastolic arterial pressure; CVP, central venous pressure; sPA, systolic pulmonary arterial pressure; dPA, diastolic pulmonary arterial pressure; WP, wedge pressure; CO, cardiac output; Tx, posttransplant; P, procainamide; M, mexiletine; A, amiodarone.

* $p < 0.01$.

† $p = 0.02$ (versus baseline and posttransplant periods).

capacity of the atrioventricular node and of the ventricle to propagate extrasystole.

Atrioventricular interval. The atrioventricular interval (AV interval) is determined by addition of the AH and HV intervals, which represent the intranodal conduction time and the His-Purkinje conduction time (specific for ventricular conduction), respectively.

The aforementioned electrophysiologic parameters were determined both in recipient and grafted hearts after transplantation and between 5 and 15 minutes after infusion of the antiarrhythmic drug.

The surface electrocardiogram, which logically pertained exclusively to the recipient heart, measured the PR interval (which includes the intraatrial, atrioventricular node, and His-Purkinje conduction times), the QRS complex (duration of intraventricular conduction), and the QT interval (which reflects the duration of ventricular depolarization and repolarization and approximates the action potential duration). These intervals were measured after transplantation and between 5 and 15 minutes after infusion of the antiarrhythmic drug.

The results have been expressed as the mean plus or minus the standard deviation. For the statistical analysis, the Mann-Whitney U test was used to compare the differences between the means of two distributions (transplanted versus recipient heart) and Wilcoxon's t test was applied to paired data (baseline period versus postadministration levels in each heart). A p value of less than 0.05 was considered to indicate significance.

Results

Procainamide. Injection of this drug produced a decrease in the cardiac output as compared with that during baseline and posttransplantation periods ($p < 0.01$) without modifying systemic, pulmonary, or wedge pressures (Table I).

With respect to the electrophysiologic study (Table II), in the recipient heart, different degrees of prolongation were detected in all the parameters studied: CL ($p < 0.01$), SACT ($p < 0.02$), ABP ($p < 0.01$), ARPAVN ($p < 0.05$), VRP ($p < 0.01$), and

AV interval ($p < 0.02$). In the surface electrocardiogram (Table III), the PR and QT intervals were prolonged ($p < 0.05$ and $p < 0.02$, respectively), whereas the QRS complex underwent no significant changes.

In the transplanted hearts, CL ($p < 0.01$), SACT ($p < 0.05$), and ARPAVN ($p < 0.01$) were prolonged. ABP, VRP, and, to a lesser degree, the AV interval were also longer, but these changes were not statistically significant (Table II).

Mexiletine. This drug produced no substantial modifications in the hemodynamic situation (Table I).

In the electrophysiologic aspect, its only effect was the moderate prolongation of the recipient heart CL ($p < 0.05$). The drug did not significantly change the atrioventricular node conduction in ARPAVN and VRP either in recipient or transplanted hearts (Tables II and III). In the transplanted hearts, the only significant change was the prolongation of the SACT, although this parameter remained at all times within the normal range and did not differ significantly with respect to findings in the recipient hearts.

Amiodarone. This drug produced a significant decrease, with respect to the baseline and posttransplantation hemodynamic situations (Table I), in the systemic arterial pressure, both diastolic and systolic ($p < 0.01$ in both cases); in the central venous pressure ($p = 0.02$) despite fluid infusion in the attempt to maintain this value constant; and in cardiac output ($p = 0.02$).

In the recipient heart (Table II), amiodarone significantly prolonged CL, ABP, ARPAVN, and VRP ($p < 0.01$ in every case), whereas SACT and AV interval were unchanged. The surface electro-

Table II. Electrophysiologic study

	CL	SACT	ABP	ARPAVN	VRP	AV interval
Procainamide						
Recipient						
Basal	346.1 ± 52.8	39.2 ± 10.5	169.2 ± 32.5	127.7 ± 32.1	144.1 ± 16.7	98.4 ± 16.2
Post	426.1 ± 61.3	49.2 ± 12.5	203 ± 37	152.3 ± 30.3	174.1 ± 26.7	107.7 ± 16.4
p Value	<0.01	<0.02	<0.01	<0.05	<0.01	<0.02
Donor						
Basal	472.3 ± 58.7	34.5 ± 10.7	220 ± 53.7	159.1 ± 34.7	178.8 ± 20.2	93 ± 9.4
Post	560 ± 66.8	43.3 ± 9.8	237.5 ± 43.3	193.3 ± 35.7	200 ± 20.6	97.7 ± 14.2
p Value	<0.01	<0.05	NS	<0.01	NS	NS
Mexiletine						
Recipient						
Basal	355.4 ± 71.1	44.5 ± 8.2	181.8 ± 40.4	133.6 ± 21.1	149 ± 22.5	108.1 ± 14
Post	385.4 ± 90.3	50.9 ± 11.3	186.3 ± 39.3	135 ± 16.5	149 ± 23.3	112.7 ± 14.9
p Value	<0.05	NS	NS	NS	NS	NS
Donor						
Basal	480 ± 62.7	33.6 ± 6.7	213.6 ± 55.1	146.3 ± 34.4	185.4 ± 21.1	104.5 ± 18.6
Post	489.1 ± 82.1	43.6 ± 9.2	213.6 ± 32.3	150.9 ± 41.1	182.7 ± 17.9	110.9 ± 13.7
p Value	NS	<0.01	NS	NS	NS	NS
Amiodarone						
Recipient						
Basal	349.1 ± 41.1	44.5 ± 12.1	168.1 ± 25.2	130.9 ± 18.6	155.4 ± 28.7	90.9 ± 10.4
Post	441.8 ± 48.5	45.4 ± 10.3	231.8 ± 25.2	150.9 ± 20.2	180.9 ± 23.8	92.7 ± 11.9
p Value	<0.01	NS	<0.01	<0.01	<0.01	NS
Donor						
Basal	496.3 ± 65.7	39.1 ± 9.4	227.2 ± 34.3	165.4 ± 24.2	208.1 ± 47.1	110 ± 20.5
Post	616 ± 122.7	47 ± 13.3	377.2 ± 78.6	268.9 ± 104.5	247 ± 60.2	130 ± 27.1
p Value	<0.01	NS	<0.01	<0.01	<0.01	<0.05

Post, After drug administration; NS, not significant.

Table III. Electrocardiographic study

	PR	QRS	QT
Procainamide			
Basal	99.2 ± 13.2	56.9 ± 11	206.9 ± 26.5
Post	106.1 ± 14.4	60 ± 11.5	224.6 ± 29
p Value	<0.05	NS	<0.02
Mexiletine			
Basal	106.3 ± 9.2	54.5 ± 9.3	211.8 ± 30.9
Post	111.8 ± 11.6	56.3 ± 8.1	213.6 ± 33.8
p Value	NS	NS	NS
Amiodarone			
Basal	93.6 ± 10.2	54.1 ± 5.8	227.2 ± 22.4
Post	102.7 ± 9	57.7 ± 9.3	263.6 ± 32.6
p Value	<0.05	NS	<0.01

Post, After drug administration; NS, not significant.

cardiogram (Table III) disclosed the prolongation of the PR and QT intervals ($p < 0.05$ and $p < 0.01$, respectively), whereas no significant modifications were detected in the QRS complex.

The effects of amiodarone on the transplanted heart (Table II) were similar to those observed in the recipient hearts, although the prolongations of CL, ABP, ARPAVN, and VRP were more marked. With regard to automaticity, the only noteworthy event was

extreme sinus bradycardia, which was produced in four cases and led to a rhythm of ventricular escape. In contrast to the findings in the recipient heart, the AV interval was also significantly longer ($p < 0.05$).

Discussion

From the clinical point of view, arrhythmias are probably generated as a consequence of the interaction of several anatomic and functional factors.¹¹ Thus it is important to determine the direct and indirect effects involved in the mechanism of action of each antiarrhythmic drug. The result will depend on the interrelationship between these two types of actions and the individual situation of each patient.

We consider the experimental model used in this study¹² to be suitable because it enabled us to compare the effects of a given drug on two hearts with different degrees of innervation that shared the same circulatory system in such a way that the serum concentrations of the drug and other metabolic products were identical. Thus the possible differences between recipients and donors could not be attributed to these levels.

In the early postoperative period, it is unusual for transplant recipients to have significant arrhythmias that necessitate intravenous antiarrhythmic therapy, and the effects of long-term oral administration of some antiarrhythmic drugs could differ from those associated with the acute intravenous setting. Nevertheless, we have considered that, even under the experimental conditions used here, the response of the conduction system of normal and denervated hearts to antiarrhythmics could bear certain relevance to the knowledge of the mechanisms of action of these drugs and to their use in transplant recipients.

Procainamide. Aside from the electrophysiologic effects associated with the class IA antiarrhythmics, the drugs in this group show peripheral and cardiac anticholinergic action, direct relaxing effects on smooth muscle, and α -adrenergic blocking. The net result depends on the strength of each specific agent in each of these aspects and the vagal tone of the individual patient to whom the drugs are administered.^{5, 13}

Procainamide exhibits weak anticholinergic and α -adrenergic blocking action. Because the sympathetic division of the autonomic nervous system predominates in the dog,¹² it could be expected that these effects of the drug would have little impact on the heart recipients in our study.

The reduction in cardiac output produced after injection of procainamide might be attributed to the negative inotropism of this drug, which is more evident when administered intravenously,^{13, 14} although the decrease in the heart rate may have played some role. The intravenous administration of procainamide is also reportedly associated with decreases in the systemic arterial pressure secondary to peripheral vasodilation resulting from α -adrenergic blockade.^{13, 15} As could be expected, under the experimental conditions established in this study, the drug did not substantially modify the peripheral vascular resistances.

From the electrophysiologic point of view, procainamide behaved in general as previously described,^{4, 13-19} depressing sinus automaticity, slowing conduction, and prolonging the refractoriness both in recipient and transplanted hearts, although in the latter the ABP, VRP, and AV interval were not significantly longer. There was no sign of facilitation of conduction caused by a vagolytic effect,¹³ perhaps for the reasons suggested previously, although a possible role for the prolongation of the QRS complex cannot be ruled out.

Mexiletine. Mexiletine has limited hemodynamic and electrophysiologic effects^{4, 13, 14, 20, 21} except when used in high doses or with rapid intravenous administration: in these circumstances the drug can produce hypotension, bradycardia, and conduction slowing.²⁰ In our study, it had no impact aside from a moderate depression of the sinus automaticity in the recipient hearts. We can offer no explanation for the prolongation of the SACT observed in the transplanted hearts, although the reduced value of this parameter in the baseline situation might suggest the existence of an entry blocker that normalized after administration of the drug.

Amiodarone. Amiodarone has a β -adrenergic blocking effect, and thus a myocardial depressant effect, although it can be counteracted by the α -adrenergic action it also possesses, reducing the peripheral vascular resistances by vasodilation.^{6, 13, 14, 20, 22} It has been reported that the myocardial depression lacks relevance in human subjects who receive long-term oral or intravenous amiodarone treatment at low doses,^{6, 22} but the antiadrenergic action appears to be more relevant during intravenous administration and in dogs. In these animals, in addition to significantly decreasing the systemic arterial pressure, amiodarone also reduces cardiac output,²² a description that coincides exactly with the findings in our study.

In the electrophysiologic aspect, amiodarone produced the expected effects in both recipient and transplanted hearts, with the effects being more marked in the latter: depression of the sinus automaticity,^{6, 14, 16, 23} prolongation of the ARPAN and VRP,* and prolongation of repolarization^{16, 17, 24, 25} as signaled by the increase in the QT interval.^{4, 6, 14, 17, 22-24}

Different reports disagree with respect to conduction slowing, a fact that may sometimes be attributed to the route of administration of the drug.^{6, 22} In the recipients in our study, neither the AV interval nor the intraventricular conduction (QRS complex) were prolonged.^{20, 25} There was, however, a moderate lengthening of the PR interval.^{14, 20} In contrast, in the donors, the AV interval was prolonged, a finding that would agree with the existence of a direct depressor effect of amiodarone on the atrioventricular nodal conduction of the impulse.^{20, 25}

According to the results obtained in this study, it can be expected that the intravenous administration of procainamide to heart transplant recipients might produce a depression of the sinus automaticity equivalent to that observed in innervated hearts, but a less

* References 4, 6, 13, 14, 16, 17, and 23 through 25.

marked effect on the conduction and refractoriness. In contrast, intravenous amiodarone administration may depress the automaticity, refractoriness, and conduction more severely in the transplant recipient. Thus its administration to this patient population, when indicated, should be done under strict control. Mexiletine did not modify the electrophysiologic parameters analyzed in the transplanted hearts. Therefore its use would be safe in the treatment of arrhythmias generated in this type of patient.

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