Procainamide Delivery to Ischemic Canine Myocardium following Rapid Intravenous Administration

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SUMMARY This study delineates the time course of procainamide accumulation in myocardium after bolus administration and its relationship to regional myocardial blood flow. The left circumflex coronary artery was ligated in 28 open-chest dogs. This was followed 40 minutes later by injection into the left atrium of labeled microspheres. 14C-labeled procainamide, 1.5 mg/kg, was then administered as a single 1-minute infusion in 24 dogs, and four dogs were killed at each of six different times (1.5-15 minutes) after onset of drug infusion. In four additional dogs, the same dose of labeled drug was administered as a 1-minute infusion repeated every 5 minutes; after the fifth dose, the animals were killed. Myocardial sections were analyzed for regional blood flow and regional procainamide concentration. In the ischemic region, procainamide accumulated more slowly, and peak concentrations were lower than in the nonischemic region, being lowest in the most severely ischemic sections. The drug was thus distributed heterogeneously through the myocardium early after bolus administration. Over time, however, this distribution became more homogenous with concentrations in nonischemic sections falling off more rapidly than in ischemic sections. Predicted steady state concentrations were achieved after 15 minutes in mildly ischemic sections (0.31-0.90 ml/min per g) but had not been reached by 25 minutes in severely ischemic sections. We conclude that ischemic myocardium, a potential site of antiarrhythmic drug action, represents a progression of pharmacokinetic compartments increasingly distal from the central compartment, depending on the severity of ischemia.

THE HEART is generally considered to be in rapid distribution equilibrium with the central pharmacokinetic compartment because it is highly perfused (Gibaldi and Perrier, 1975; Koch-Weser, 1977). However, if the rate of drug equilibration between plasma and myocardium is related to perfusion, then ischemic areas of myocardium should behave as peripheral pharmacokinetic compartments. Depending on their blood flow, such areas might therefore be classifiable as more proximal or more distal, that is, requiring less or more time to equilibrate with the central compartment.

Because ventricular premature depolarizations in patients with coronary artery disease probably originate from areas of ischemic myocardium (Waldo and Kaiser, 1973; Boineau and Cox, 1973), the sites of action of antiarrhythmic drugs may be in peripheral pharmacokinetic compartments. Using the R-V interval of coupled premature ventricular depolarizations as a measure of drug effect, Giardina and Bigger (1973) analyzed the response of patients given repeated 1-minute infusions of procainamide every 5 minutes and observed that in most patients the drug probably continued to accumulate over the 5-minute time course. Based on those findings, they postulated that procainamide's site of action was in a peripheral compartment. To validate their hypothesis and to evaluate whether the magnitude of reduction in myocardial blood flow is related to the manner in which procainamide accumulates in the myocardium, we investigated the temporal relationship between rapid intravenous infusion of drug and its resultant concentration in nonischemic and ischemic myocardium. Our results demonstrate that, for procainamide, ischemic myocardium functions as a series of peripheral compartments which can be characterized by their myocardial blood flows.

Methods

Twenty-eight mongrel dogs weighing 14-20 kg were anesthetized with a-chloralose, 85 mg/kg, iv, intubated with auffed endotracheal tube, and ventilated with a Harvard Apparatus respiration pump. The right femoral artery was exposed, and a polyvinyl chloride catheter with an outside diame-
ter of 3 mm was introduced into the vessel, advanced to the ascending aorta, and connected to a Statham P23Db pressure transducer. Phasic and mean aortic blood pressure and the ECG (lead II) were recorded on an Electronics for Medicine DR-8 recorder. A catheter was passed into the bladder and secured to prevent leakage and to provide continuous drainage. A left thoracotomy then was performed, and a catheter was inserted into the left atrium and secured by a purse-string suture.

The left circumflex coronary artery was ligated within 1.5 cm of its origin. Forty minutes after coronary artery ligation, approximately $4 \times 10^{10}$ $^{51}$Cr-labeled microspheres (3M Co.) with diameters of 7–10 µm were injected into the left atrium over 45 seconds. At the same time, to provide reference blood samples, blood was withdrawn continuously at 12 ml/min over a 2-minute period through the aortic catheter using a Harvard Apparatus peristaltic pump. At 45 minutes after coronary artery ligation, procainamide, 1.5 mg/kg, was infused over 1 minute, using a Harvard Apparatus infusion pump. Procainamide solution for infusion was prepared in the following manner: 50 µCi of $^{14}$C procainamide ($^{14}$C-procainamide (carboxyl-$^{14}$C), 4.83 µCi/mg, New England Nuclear) was added to the additional amount of procainamide required for the 1.5 mg/kg infusion and diluted with saline to a final volume of 20 ml.

Four dogs were killed at each of the following times after the onset of procainamide infusion: 1.5, 2, 3, 4, 5, and 15 minutes. Just prior to death, blood samples for analysis of plasma procainamide concentration were obtained through the aortic catheter using a Harvard Apparatus peristaltic pump. The heart then was excised, and the right atrium, left atrium, and right ventricle (free wall) were rapidly dissected away from the left ventricle. The left ventricle was immediately frozen in a dry ice-ethanol mixture ($-37^\circ$C). All samples were stored at $-5^\circ$ C.

A second set of experiments was designed to simulate a method by which procainamide is administered in the clinical setting. Four dogs were prepared as above, but instead of receiving a single infusion of procainamide, they were given a 1-minute infusion of procainamide, 1.5 mg/kg, every 5 minutes for a total of 5 infusions (total dose = 7.5 mg/kg). Blood samples for analysis of procainamide concentration were withdrawn at the end of each 1-minute infusion and just prior to the subsequent infusion. Additional samples were obtained 2 minutes after onset of the first dose and every minute following the last infusion. Five minutes after the final infusion, a 25-minute blood sample was withdrawn, and the heart was excised and stored as above.

Left ventricular tissue samples for analysis of $^{14}$C and $^{51}$Cr were obtained as follows: the left ventricular posteroseptal and lateral border zones and the apex and base were discarded, leaving an anterosep-

tal nonischemic control region and a posterolateral ischemic region. The ischemic region was divided into posterior, posterior papillary, and lateral transmural segments. Each segment was subdivided into four layers of equal thickness from epicardium to endocardium. Each of the four control and 12 ischemic layers was further sectioned by a diagonal cut so that each resulting triangle would have equal representation from the inner and outer surface of the section. Two samples were obtained from the long side of each triangle and used for analysis of $^{14}$C.

The analysis of $^{14}$C in the duplicate samples was performed as previously described (Strauss et al., 1978) using a combustion technique to liberate $^{14}$CO$_2$, which was then trapped in solution and counted in a Beckman model LS 100C liquid scintillation spectrometer. Procainamide concentration ($\mu g/g$ sample weight) in each sample was determined using the formula: $[PA]\mu g/g = [unlabeled\ PA (\mu g)\ in\ infusion labeled\ PA (dpm)\ in\ infusion] \times [^{14}C\ (dpm)\ in\ sample/weight\ of\ sample\ (g)]$. The myocardial procainamide concentrations from the two samples of each section were used to calculate a mean value for myocardial procainamide concentration in each section. No adjustment was made for $N$-acetylprocainamide, since this metabolite is not formed in the dog (Dreyfuss et al., 1971).

Portions of triangular subsections of the left ventricle not used in the analysis of $^{14}$C were used to analyze $^{51}$Cr. Blood reference and myocardial samples were packed in vials and counted in a $\gamma$ spectrometer with corrections made for background. Blood flow (ml/min) to each section was determined using the formula: $F_X = F_R \times C_M + C_R$, where $F_M = tissue\ sample\ blood\ flow, F_R = reference\ blood\ flow, C_M = tissue\ sample\ counts/min, and C_R = reference\ counts/min$. Sample blood flow was divided by sample weight to express flow as ml/min per g of tissue.

**Statistical Methods**

The data were described by the lower tertile, median, and upper tertile, where lower tertile is the 33 1/3 percentile of drug concentration and upper tertile is the 66 2/3 percentile of drug concentration. The data were summarized in this manner, rather than as mean and standard deviation or standard error, because in many instances the data did not have a symmetric distribution; also, standard errors are not a fair measure of variability within a flow group, because such use gives equal weight to measurements made from the same dog and to measurements from different dogs.

Myocardial drug concentration vs. blood flow relationships for the different times after drug administration were studied as follows: for each of the 28 dogs, a quadratic function of the form $af^2 + bf + c$ (where $F = myocardial\ blood\ flow$) was fitted to the normalized drug concentration vs. myocar-
Figure 1 Normalized myocardial procainamide concentration plotted as a function of regional myocardial blood flow in two dogs. Data from a dog killed 2 minutes (panel A) and 15 minutes (panel B) after onset of drug infusion. The parameters which best fit the data from each experiment are given and are used to generate the quadratic curve shown in each panel. Median control myocardial procainamide concentrations were 9.22 μg/g in panel A and 1.82 μg/g in panel B. The areas under each curve (between 0.0 and 0.8 ml/min per g) are 33.8 in panel A and 49.5 in panel B. 

Median flows in the groups were 0.04 ml/min per g, 0.22 ml/min per g, and 0.52 ml/min per g, respectively.

Plasma Procainamide Concentrations

The plasma procainamide concentrations obtained from both sets of experiments are depicted in Figure 2, A and B. In the single bolus experiments at 1.5 minutes after onset of procainamide infusion, the median plasma procainamide concentration was

Results

Myocardial Blood Flow

Median (lower tertile, upper tertile) myocardial blood flow for all dogs in the anteroseptal nonischemic (control) region was 1.09 (1.03, 1.27) ml/min per g. Myocardial blood flow in the posterolateral ischemic region ranged from 0.00 ml/min per g to control values, with most sections having flows of less than 0.3 ml/min per g. The ischemic sections were grouped as follows: marked ischemia, 0–0.15 ml/min per g; moderate ischemia, 0.16–0.30 ml/min per g; and mild ischemia, 0.31–0.90 ml/min per g.

Figure 2 Plasma procainamide concentrations at the time of death in 24 dogs given a single infusion of procainamide, 1.5 mg/kg, over 1 minute are shown in panel A. Plasma procainamide concentrations in four dogs during periodic administration of procainamide, 1.5 mg/kg, over 1 minute repeated every 5 minutes are shown in panel B. Note that the initial sampling time is 1.5 minutes in panel A as opposed to 1 minute in panel B. Horizontal bars indicate period of drug infusion. Data are expressed as the median and tertiles.
Non-ischemic Region
0.31-0.90 ml/min/g
0.16-0.30 ml/min/g
0.00-0.15 ml/min/g
Median and Tertiles

Ischemic Region

Time (min)

FIGURE 3 Myocardial procainamide concentrations plotted as a function of time following a 1-minute infusion of procainamide. The data from the ischemic sections were grouped by flow. The horizontal bar indicates the period of drug infusion. Data are expressed as median and tertiles.

8.10 μg/ml; at 2 minutes, 3.12 μg/ml; at 3 minutes, 1.80 μg/ml; at 4 minutes, 1.64 μg/ml; at 5 minutes, 1.47 μg/ml; and at 15 minutes, 0.55 μg/ml. In the periodic bolus experiments, the median plasma procainamide concentration at time of death was 5.07 μg/ml.

Myocardial Procainamide Concentrations

In the 24 dogs killed serially between 1.5 and 15 minutes after onset of drug infusion, median myocardial procainamide concentrations in the nonischemic region reached a peak of 8.52 μg/g at 2 minutes and declined to 1.71 μg/g by 15 minutes (Fig. 3). At each time, reduced drug concentration in ischemic sections was associated with reduced myocardial blood flow. Also, the pattern of sharp rise and rapid decline of myocardial procainamide concentration seen in the nonischemic region was blunted in the ischemic region and was especially flat in the lowest flow sections (Fig. 3).

In the periodic bolus experiments, median myocardial procainamide concentration at 25 minutes was 18.86 μg/g in the control region (Table 1). Although the myocardial procainamide concentration was always lower in regions of reduced myocardial blood flow, the reduction in drug concentration in the moderate and marked ischemia groups as compared with control was less at 25 minutes than at earlier times. This is best illustrated in Figure 4. Dogs killed at different times after drug administration had different control myocardial procainamide concentrations. To facilitate comparison of ischemic myocardial drug concentrations among dogs, the data were normalized. This was done by dividing the mean drug concentration from the ischemic region of each experiment by that in

<table>
<thead>
<tr>
<th>Table 1</th>
<th>Procainamide Concentrations following Drug Administration</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>5 min</td>
</tr>
<tr>
<td>([PA]_{I5} ) (μg/ml)</td>
<td>1.47 (1.24, 1.69)</td>
</tr>
<tr>
<td>([PA]_{I0} ) nonischemic region (μg/g)</td>
<td>7.02 (6.62, 7.43)</td>
</tr>
<tr>
<td>([PA]_{I5} ) ischemic region, 1 (μg/g)</td>
<td>0.45 (0.33, 0.55)</td>
</tr>
<tr>
<td>([PA]_{I0} ) ischemic region, 2 (μg/g)</td>
<td>2.14 (1.90, 2.38)</td>
</tr>
<tr>
<td>([PA]_{I5} ) ischemic region, 3 (μg/g)</td>
<td>3.81 (2.97, 4.82)</td>
</tr>
</tbody>
</table>

Data are expressed as median and tertiles. Times correspond to intervals after onset of single (5-min) and periodic bolus (25-min) administration of procainamide. Results are grouped into ischemic regions based on regional myocardial blood flows of 0.00-0.15, 0.16-0.30, and 0.31-0.90 ml/min per g, respectively. Abbreviations: \([PA]_{I5} \) = regional myocardial procainamide concentration; \([PA]_{I0} \) = plasma procainamide concentration.
the control region and then multiplying by 100. Drug concentrations from ischemic sections were thus expressed as a percentage of the control concentration. This normalized myocardial procainamide concentration is plotted on the ordinate in Figure 4; the time after onset of drug administration is on the abscissa. In the two lowest flow compartments, the normalized drug concentration continued to rise up to and after 25 minutes; in the mildly ischemic compartment, however, maximal values were reached by 15 minutes.

A comparison of the myocardial procainamide concentrations at 5 minutes and 25 minutes is also given in Table 1. The considerable differences in drug concentrations between well-perfused and poorly perfused regions at 5 minutes (Fig. 4, Table 1) had diminished by 25 minutes. This is due to the fact that the percent increase in myocardial procainamide concentration from 5 minutes to 25 minutes was most marked in sections receiving the lowest flows (Table 1); that is, over time, drug distributed toward the more ischemic compartments.

Relationship of Myocardial Procainamide Concentration to Regional Myocardial Blood Flow at Different Times following Drug Administration

For each dog, the normalized myocardial procainamide concentrations and myocardial blood flows from the sections were fitted to a quadratic curve (Fig. 1). Squared multiple correlation coefficients for these curves indicated good fits, ranging from 0.71 to 0.996. The area under this curve for each dog was used to describe the overall curve. These areas at different times following drug infusion were then compared (Fig. 5). Between 1.5 and 25 minutes after onset of drug administration, the area under the curve increased significantly with time. That is, the longer the time following drug administration, the higher was the normalized myocardial procainamide concentration at any given blood flow (normal scores correlation, \( P < 0.01 \)).

Discussion

Our results demonstrate that ischemic areas of myocardium act as peripheral compartments for procainamide delivery and that the time course of drug accumulation following bolus administration is related to regional myocardial blood flow. In the anterior control region, changes in drug concentration over time rapidly followed changes in plasma procainamide concentration, since drug concentration in this region reached a peak 30 seconds following termination of drug infusion and then declined rapidly. In the ischemic region, changes in drug concentration reflected changes in plasma concentration less closely (Fig. 2). Accumulation of drug was decreased and decline in procainamide concentration was more gradual in ischemic myocardium as compared with the nonischemic region, suggesting that areas of myocardium that are hypoperfused behave pharmacokinetically as peripheral compartments.

When the myocardial procainamide concentration in each flow group 5 minutes after a single bolus is compared to concentration 5 minutes after the last of five boluses administered 5 minutes apart, it is evident that the percent increase in drug concentration from 5 to 25 minutes was least for plasma and the nonischemic region and became progressively greater in regions of decreasing myocardial blood flow (Table 1). As a result, the 16-fold difference in concentration between the nonischemic and most ischemic region at 5 minutes after onset of drug infusion (7.02 vs. 0.45 \( \mu \)g/g) had narrowed to a 3-fold difference at 25 minutes (18.86 vs. 6.03 \( \mu \)g/g). This relative distribution of drug toward the most ischemic regions of myocardium with time is consistent with the conclusion that increasingly ischemic regions function as increasingly distal kinetic compartments with regard to net procainamide accumulation.

In a previous study in which procainamide was infused continuously over a 4-hour period to approximate pseudo-steady state conditions and drug concentrations then obtained, we demonstrated that ischemic areas of myocardium will eventually have substantial concentrations of procainamide.
(Wenger et al., 1978). In Figure 4, the data from that study are plotted along with the results from the present experiments. As can be seen, concentrations of procainamide in the mildly ischemic sections approach steady state values earlier than concentrations in markedly ischemic sections of myocardium. Mildly ischemic sections reach steady state values at 15-25 minutes. Thus, if procainamide were to have its site of action in a region of mildly ischemic myocardium, one might expect that a concentration-response evaluation made less than 15 minutes after onset of administration of procainamide at a constant rate (continuous or discrete) would fail to represent the concentration-response relationship seen at steady state. If the site of action of the drug were in more ischemic regions, concentration-response relationships might well not reach steady state conditions until 25 minutes or more after onset of constant rate administration.

A perfusion-limited model of drug disposition kinetics has previously been described (Price et al., 1960; Bischoff and Dedrick, 1968; Bischoff et al., 1971). This model predicts the time course of drug distribution to various organs having different blood flows and different steady state distribution ratios of drug between tissues and plasma. Benowitz et al. (1974) applied this mathematical analysis to bolus administration of lidocaine in monkeys. The effect of different organ blood flows on the predicted tissue concentration vs. time curves calculated by this model is similar to the effect of different myocardial blood flows on the measured tissue procainamide vs. time data that we observed in the present study.

Galeazzi et al. (1976) noted that the effect of procainamide on the time course of Q-T prolongation in healthy human volunteers lagged behind the drug concentration vs. time curve in plasma so that a plot of plasma procainamide concentration vs. Q-T prolongation over time resulted in a counter clockwise hysteresis loop. Giardina et al. (1973) and Elson et al. (1975) have demonstrated, after bolus administration of procainamide to patients, the reappearance of ventricular arrhythmias at plasma procainamide concentrations that are lower than those at which they disappeared. There are at least four explanations for this observation of arrhythmia suppression onset-offset hysteresis: (1) An active metabolite is formed in man that accumulates during the fall in plasma drug concentration. (2) The onset of effect and termination of effect of a drug at its site of action is delayed. (3) The amount of drug needed to eliminate an arrhythmia is greater than the amount needed to keep it suppressed. (4) The arrhythmia arises from a pharmacokinetic compartment distal to the central compartment so that a slowly equilibrating peripheral compartment of procainamide concentration does not reflect the drug concentration at its site of action. Our data demonstrate that, if the arrhythmia originates from ischemic myocardium and the drug is given as a rapid intravenous infusion, the inequality between plasma concentrations at onset and offset of antiarrhythmic effect of procainamide would, at least in part, be due to the time needed for the drug to get to a distal compartment.

To study the effect of antiarrhythmic drugs in canine acute myocardial infarction, Kupersmith et al. (1975) measured changes in effective refractory period from ischemic myocardium following a bolus plus continuous infusion of lidocaine, a protocol designed to achieve a constant plasma concentration of drug. Despite the fact that plasma lidocaine concentration was stable for most of the 2-hour infusion time, effective refractory period of the ischemic zone became increasingly prolonged throughout the duration of the infusion. They explained the gradual onset of lidocaine effect by delayed delivery of drug to the deep layers of infarcted myocardium in which the electrodes were placed. Our data are consistent with their results.

Our results also support the conclusion of Giardina and Bigger (1973) regarding the site of action of procainamide in the treatment of coupled premature ventricular depolarizations. In seven patients given a 1-minute infusion of procainamide every 5 minutes until coupled premature ventricular depolarizations were abolished, the coupling interval increased as the premature ventricular depolarization frequency decreased. This suggested that procainamide was gradually prolonging conduction in the depressed portion of a reentrant pathway until block finally occurred and the arrhythmia stopped. Assuming that prolongation of the coupling interval reflected procainamide effect at its site of action, these investigators postulated that, if the drug acted in the central compartment, then the coupling interval would decrease from the termination of drug infusion to the end of the 5-minute period, correlating with the falling plasma procainamide concentration. On the other hand, if the site of action were in a slowly equilibrating peripheral compartment (what we have called here a distal compartment), then the coupling interval would progressively increase during the 5 minutes following drug injection. If the site of action were located in a rapidly equilibrating (i.e., proximal) compartment, then the coupling interval might at first increase but then decrease during the 5-minute period. In five of their seven patients, the coupling intervals prolonged over the 5 minutes following drug infusion, suggesting that the site of action was in a distal compartment. Four of these five patients had arteriosclerotic heart disease, and the fifth had heart disease of unknown cause. In the other two patients, one with heart disease of unknown cause and the other with rheumatic heart disease, the R-V coupling interval at first prolonged but then shortened, as might be expected if the site of action were a well-perfused proximal compartment.

A substantial body of evidence suggests that
many arrhythmias associated with ischemic heart disease arise in areas of nonhomogeneous infarction or at border zone areas between infarcted and normal myocardium. Such areas are not likely to receive blood flows as low as our markedly ischemic sections, since flows of 0.15 ml/min per g or less result in almost total infarction of the area (Irvin and Cobb, 1977). Electrophysiologically viable fibers in mildly or moderately ischemic regions may well be important sites of origin of ischemic arrhythmias and presumably are the sites of action of antiarrhythmic drugs. Our data demonstrate that these regions of myocardium behave as peripheral pharmacokinetic compartments; the relative proximity of these compartments to the central compartment can be characterized by the myocardial blood flow.

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