

# The Pharmacology and Clinical Use of Lidocaine and Procainamide\*

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Both procainamide and lidocaine are useful for acutely treating cardiac arrhythmias, and procainamide can be useful in chronic antiarrhythmic regimens. Successful management of cardiac arrhythmias requires knowledge of: 1) the mechanism and natural history of the arrhythmia, 2) the physiologic state of the patient, and 3) the cardiac effects, pharmacodynamics, and general pharmacology of the antiarrhythmic drugs.

Although often done, it is foolhardy to undertake treatment of a cardiac arrhythmia without a precise diagnosis. The rationalization for such an undertaking frequently is that, no matter which of several possible arrhythmias is at hand, the treatment to be initiated would be beneficial or at least not harmful for any. This rationalization is often invoked to avoid

the considerable effort which may be required in order to precisely diagnose the nature of the arrhythmia. There are many specific cases where one not only treats a harmless arrhythmia, or, by not making a diagnosis, fails to use the correct therapy, but also employs a therapy which is actually harmful. Figure 1 shows an example of unnecessary therapy on the basis of an error in diagnosis. This patient had occasional ventricular premature depolarizations (VPD's). The VPD's were often followed by an aberrantly conducted beat of supraventricular origin. These couplets of wide QRS's were incorrectly considered to be salvos of VPD's and were treated with lidocaine. In fact, the patient had no indication for antiarrhythmic drug therapy at all. As luck would have it, lidocaine caused undesirable central nervous system effects in this patient. As mentioned above, therapy may be not only inappropriate but also damaging. For example, patients with atrial flutter with variable A-V conduction not infrequently show wide aberrant beats. In intensive care units, these are often mistakenly called VPD's. The fact that a non-standard bipolar chest lead is used for monitoring may obscure the fact that the beat has a RBBB configuration, a finding which might lead the physician to suspect aberrant conduction. Also, treatment may be initiated on the basis of observation of the rhythm on the oscilloscope screen. Thus, the physician may overlook the typical group beating of the Gouaux-

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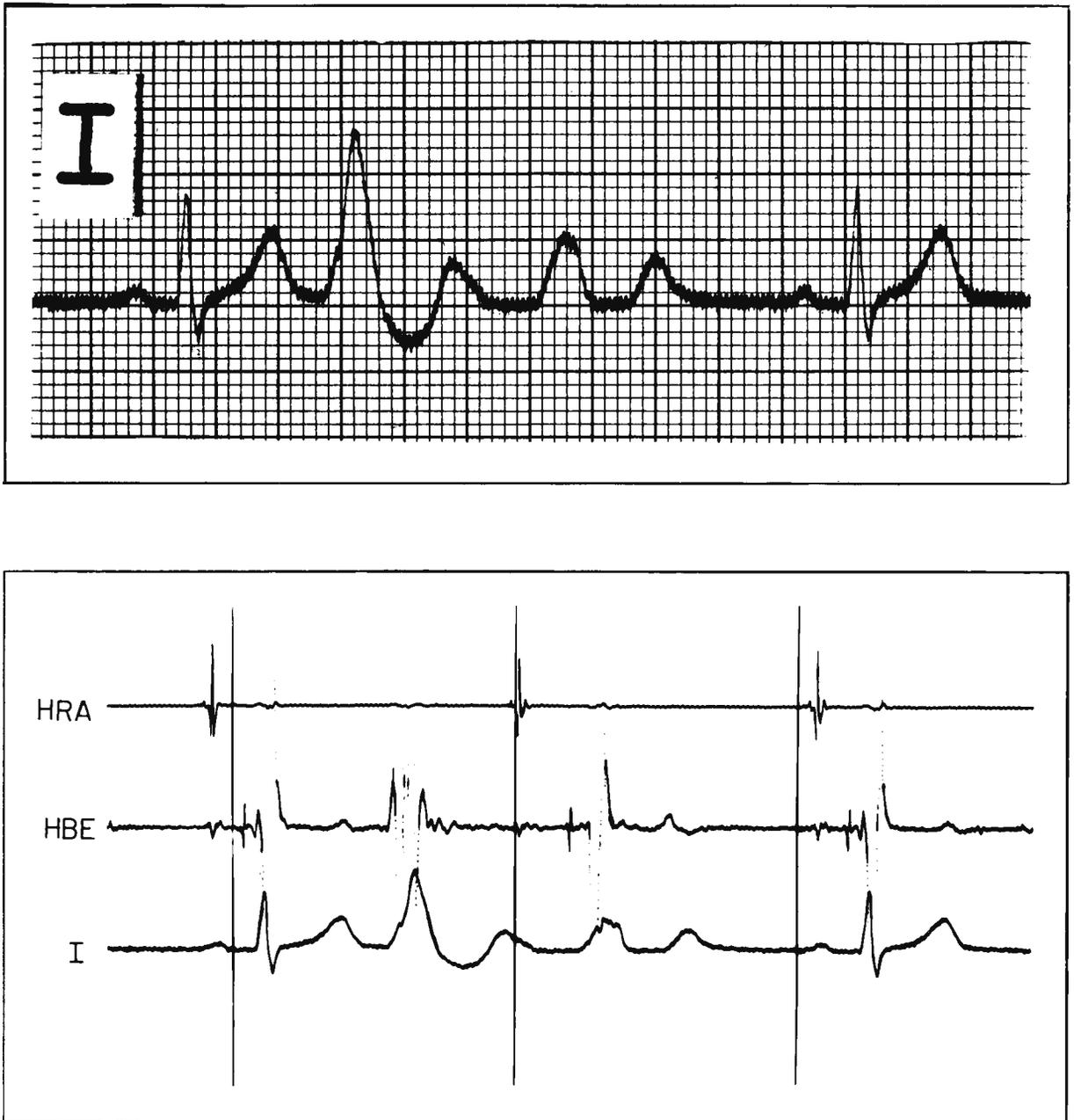


Fig. 1—Incorrect interpretation of rhythm leading to unnecessary therapy. The *upper* panel shows lead I of the ECG which was incorrectly interpreted as salvos of VPD's, and on this basis lidocaine was begun.

The *lower* panel shows recordings from high right atrium (HRA), the bundle of His (HBE), and lead I of the ECG. Actually, the rhythm was occasional VPD's with concealed retrograde conduction resulting in aberrant conduction of the subsequent beat (LBBB configuration).

Ashman phenomenon which would have been more obvious in analyzing a paper recording. This combination of errors in the intensive care unit can cause aberrant beats to be treated with lidocaine. Lidocaine can slow the atrial rate and enhance A-V conductivity, leading to a striking increase in ventricular rate. Lidocaine in these circumstances has caused atrial flutter to conduct with a 1:1 A-V ratio and has produced ventricular rates of nearly 300 per minute. If the heart is hemodynamically impaired, rapid heart rates caused in this way can be catastrophic. Other examples could be given, but these two suffice to underscore the importance of obtaining a correct diagnosis of the arrhythmia before embarking on a therapeutic course.

Even after precise identification, obviously, not all arrhythmias deserve treatment with suppressant antiarrhythmic drugs. Many arrhythmias do not deserve any therapy whatsoever. The past decade of coronary care unit experience has taught us a great deal about the natural history and indications for treating arrhythmias which arise between 4 and 72 hours after onset of symptoms in acute myocardial infarction. A great error which has become a national epidemic has been the unjustifiable extrapolation of the CCU experience to the first two hours of infarction or of the late postinfarction period. At both of these times the pattern arrhythmias, their meaning, or their response to therapy seem to be very different from arrhythmias encountered in the CCU and, at present, less well characterized. Even worse, there is a widespread tendency in recent years to use the same criteria for treating arrhythmias in other etiologic forms of heart disease as those used in acute myocardial infarction. In most forms of heart disease, our knowledge of the meaning and natural history of arrhythmias is even more rudimentary than our knowledge of arrhythmias in various stages of coronary heart disease. However, in many diseases, it is abundantly clear that arrhythmias do not need treatment even though the same ECG pattern would dictate therapy in acute myocardial infarction.

Once an arrhythmia is identified and the need for treatment established, the regimen of therapy may or may not require a specific antiarrhythmic drug. Arrhythmias encountered outside the coronary care unit very often are caused or seriously aggravated by non-cardiac factors such as electrolyte, acid-base, or blood gas derangements or drug toxicity. When initially evaluating any cardiac arrhythmia, the physician should consider the many possible non-

cardiac causes and institute the appropriate clinical and laboratory investigations to identify these, even though temporary emergency therapy is required immediately. Not only will correction of non-cardiac causes usually control the arrhythmia but also arrhythmias generated by electrolyte imbalance or blood gas derangement may be highly resistant to "specific" antiarrhythmic drugs like procainamide or lidocaine.

When a drug is finally selected to treat an arrhythmia, the goal is to maintain the plasma concentration above the minimum effective concentration without inadvertently producing toxic concentrations. To successfully achieve this goal requires a considerable knowledge about the pharmacokinetics, metabolism, and excretion of the drugs utilized.

It is our purpose to discuss briefly the clinically relevant electrophysiologic properties, clinical usage, pharmacodynamics, and toxicity of procainamide and lidocaine.

**Electrophysiologic Properties.** The following are a few clinically relevant electrophysiologic effects of procainamide and lidocaine.

*Lidocaine.* Lidocaine is a Group II antiarrhythmic drug. It suppresses automaticity in cardiac Purkinje fibers by increasing the potassium conductance of the sarcolemma but does not significantly alter threshold voltage. It shortens action potential duration and refractoriness in Purkinje fibers and ventricular muscle but has practically no effect on atrial tissues. It does not alter conduction velocity or responsiveness very much in either normal atrial or normal ventricular tissues. Under certain circumstances, lidocaine can improve conduction or reverse conduction block in ventricular tissues. Lidocaine depresses sinus node function less than procainamide. Rarely, it has been reported to suppress sinus function, usually in older patients, particularly with inferior myocardial infarction and/or preexisting signs of sinus node dysfunction. Lidocaine has little effect on atrial arrhythmias as might be predicted from its lack of effect on atrial tissues from normal animals. The drug can, but does not always, cause slight slowing of atrial rate in atrial flutter. Also, lidocaine causes no change or decrease in A-V conduction time and A-V refractoriness. Since the drug does not prolong conduction in the ventricular tissues, it does not prolong the QRS, and since it does not prolong action potential duration in the ventricles, it does not prolong the QT. It is still not clear how lidocaine abolishes reentrant ventricular arrhythmias in man.

Our studies to date suggest that it may do so either by improving conduction throughout the reentrant circuit or by blocking conduction in abnormal components of the circuit without affecting normal components.

**Procainamide.** Procainamide (like quinidine) is a typical Group I antiarrhythmic drug. It suppresses automaticity and moves the threshold voltage of heart muscle toward zero. Also, it lengthens action potential duration and lengthens the refractory period of atrial and ventricular cell types. It slows conduction in the atrium, A-V node, and ventricle and decreases membrane responsiveness of atrial and ventricular fibers. Many of these actions are reflected in the ECG. Procainamide does not usually affect the sinoatrial rate in intact man, but it can cause dramatic slowing of sinus rhythm in patients with derangements of sinus node function. This drug often causes minimal flattening and widening of the P wave. The atrial rate is slowed by procainamide in atrial fibrillation and flutter, and high concentrations will convert these rhythms to sinus rhythm. A direct action of procainamide is to slow A-V conduction and increase the refractoriness of the A-V conducting system; the magnitude of this effect is quite variable from patient to patient under similar conditions and

is modified by many other variable factors. Administration of procainamide to treat VPD's caused by digitalis toxicity may unpredictably produce severe A-V conduction disturbances. Slowing of conduction in the His-Purkinje system and in ordinary ventricular muscle caused by this drug is reflected in a widening of the QRS interval. In a given patient, QRS width changes usually increase linearly as a function of plasma drug concentration. The changes in repolarization produced by procainamide usually cause prolongation of the QT interval and alteration in T wave contour. The rather reliable change in QRS and QT intervals has proved quite useful in estimating therapeutic and toxic cardiac effects during therapy. The profound changes procainamide causes in conduction, responsiveness, and refractoriness of ventricular tissues no doubt underly its impressive ability to suppress VPD's or ventricular tachycardia. Our recent experiments in man suggest that as the plasma concentration of this drug rises, it causes a steadily increasing depression of conduction in a ventricular reentrant circuit until conduction fails altogether and the arrhythmia is abolished.

**Clinical Use. Lidocaine.** Lidocaine is not effective against a wide variety of cardiac arrhythmias, being most useful in combatting ventricular arrhythmias.

TABLE 1.  
Effectiveness of Lidocaine and Procainamide Against Cardiac Arrhythmias\*

ARRHYTHMIA	LIDOCAINE		PROCAINAMIDE	
	# of Success/# of Cases		# of Success/# of Cases	
<b>SUPRAVENTRICULAR:</b>				
Atrial premature depolarizations	15/ 31	(48%)	8/ 13	(62%)
Paroxysmal supraventricular tachycardia	5/ 11	(46%)	28/ 40	(70%)
Supraventricular tachycardia with A-V block	0/ 4	—	—	—
Atrial flutter	0/ 11	( 0%)	14/ 53	(26%)
Atrial fibrillation	3/ 41	( 7%)	73/215	(34%)
A-V junctional premature contractions	4/ 8	(50%)	9/ 13	(69%)
Non-paroxysmal A-V junctional tachycardia	0/ 7	( 0%)	26/ 33	(79%)
Unspecified supraventricular tachycardia	3/ 9	(33%)	14/ 23	(61%)
Total:	30/122	(25%)	172/390	(44%)
<b>VENTRICULAR:</b>				
Ventricular premature contractions	389/495	(79%)	210/244	(86%)
Ventricular tachycardia	48/ 69	(70%)	98/122	(80%)
Total:	437/564	(77%)	308/366	(84%)

\* A comparison of clinical effectiveness of lidocaine and procainamide against supraventricular and ventricular arrhythmias. Calculations are based on a review of the literature up to 1972 and include arrhythmias that were completely suppressed or at least 90% improved after drug therapy. The percentage was not determined where total cases were less than five.

mias. It is practically worthless against atrial flutter or fibrillation (Table 1); the rare instances in which it appears to abolish one of these rhythms may only be due to coincidence, or to indirect effects. Lidocaine is also, as a rule, ineffective against atrial or A-V junctional tachycardias unless they are caused by digitalis excess. Of course, lidocaine is highly effective against ventricular arrhythmias arising in many circumstances, but it is limited to relatively short-term use because it must be administered parenterally.

It should be emphasized that there is considerable difference in electrophysiologic action between procainamide and lidocaine, and it is common to see an arrhythmia that is resistant to one, submit to the other.

*Procainamide.* Procainamide is an antiarrhythmic drug of broad spectrum, effective against a wide variety of atrial, A-V junctional, and ventricular arrhythmias (Table 1). In general, higher plasma concentrations are required to convert or prevent atrial fibrillation than those needed to control ventricular arrhythmias. Early in its use, this fact led to the mistaken impression that the drug was ineffective against atrial arrhythmias. However, as will be discussed later, procainamide has a short half-life which means to continuously maintain plasma concentrations effective against atrial arrhythmias requires large doses every six hours. Large doses may produce toxic peak concentrations and necessitate more frequent dosing, a change which is usually inconvenient for the patient. This drug is a poor choice against ventricular arrhythmias in patients with severe A-V conduction disturbances because it may worsen conduction. Although it can be effective against many digitalis-toxic arrhythmias, its actions in this circumstance are too unpredictable to warrant its use.

*Prophylaxis.* In very recent years, studies have evaluated prophylactic use of procainamide or lidocaine, as well as other antiarrhythmic drugs, in the CCU. These studies, conducted in first-rate university hospitals, fail to show a decrease in mortality in the treated versus the control group. This might be expected since patients with heart failure, shock, sinus bradycardia, A-V block, or arrhythmias requiring immediate treatment were not admitted to the studies. Furthermore, these CCU's were all well-staffed so that sophisticated hospital-based physicians were almost instantly available to analyze and treat arrhythmias which developed in either the placebo or drug-treated group. It would seem that a pa-

tient in a university hospital CCU has little to gain from prophylactic therapy. On the other hand, a patient residing in any one of the many community hospital CCU's in this country where the staff may be less plentiful or well-trained and the patient's physician is based in his office practice, might have a great deal to gain from routine prophylaxis. Prophylaxis might prevent harmful results where premonitory arrhythmias were overlooked. However, routine prophylaxis in every case of myocardial infarction might increase the morbidity and mortality in patients with cardiac failure or shock, or those with bradyarrhythmias or conduction defects. Thus, even in community hospitals, the case for routine prophylaxis in acute myocardial infarction is not entirely clear.

Prophylaxis for arrhythmias in ambulatory, apparently well patients with coronary heart disease is even less well-grounded than prophylaxis in acute myocardial infarction. Several pertinent facts are emerging. First, VPD's are extremely common in asymptomatic coronary heart disease patients. Second, middle-aged men who have frequent VPD's (>10 VPD's per 1,000 beats) or sustained relative bradycardia have a much higher incidence of sudden death in follow-up periods than their peers without one of these two rhythm disturbances, even though neither group has clinically evident coronary heart disease. What is not clear is whether any available drug can significantly and persistently reduce the incidence of these arrhythmias for long periods of time without undue undesirable effects. Neither is it clear that, if one could alter these arrhythmias that are correlated with sudden death, the incidence of sudden death would be reduced. Thus, at present, prophylaxis in such a population is highly experimental and should be controlled since we do not even know that prophylaxis would do more good than harm.

Another related area of current interest arises from the fact that patients who die from arrhythmias during early stages of acute myocardial infarction or ischemia probably suffer from either ventricular fibrillation or bradyarrhythmias. It has been suggested that patients who are known to be at risk to myocardial ischemia, that is, patients with known coronary heart disease, carry syringes containing lidocaine and/or atropine. These patients would be advised, on experiencing symptoms of myocardial ischemia, to inject their drug intramuscularly and come to the hospital. Again, with the evidence avail-

able at present, we are not certain that such a course of action would not be more harmful than helpful, and such therapy cannot be recommended for more than controlled trials. However, it is reasonable to urge immediate contact between the patient with coronary heart disease who has a change in symptoms and the health care system. Analysis of the ECG either transmitted by telephone or obtained by a medical team invading the community would allow early specific treatment on the basis of the arrhythmias encountered in the individual patient. Some variant of this method would seem greatly preferable to self-injection of drug or drugs initiated on the basis of symptoms alone without regard for the presence or type of rhythm disturbance.

**Pharmacodynamic Considerations.** Particularly in treatment of acute arrhythmias, one of the most important aspects of antiarrhythmic drug therapy is pharmacodynamics. It is necessary to maintain the plasma drug level above the minimum effective concentration (MEC) because life-threatening arrhythmias may emerge when plasma concentrations dip below this level. Also, the rate at which MEC is achieved may be quite important. Knowledge of drug kinetics is even necessary in order to assess the effectiveness of the drug being used. Lack of a consummate knowledge of pharmacodynamics often leads physicians to conclude that a particular drug is ineffective in combatting a particular arrhythmia. In actuality, this conclusion is often incorrect because the physician is unaware of the expected time course of drug action and thus evaluates drug effectiveness at an inappropriate time. Since many of the arrhythmias treated in emergency situations, for example, acute myocardial infarction, are short-lived, the need for antiarrhythmic drug therapy is brief. Usually, a few days of such therapy is sufficient. When discontinuing or interrupting the antiarrhythmic drug therapy under such circumstances, knowledge of the expected course of elimination is vital. This knowledge allows maximum intensity of observation at appropriate times without wasting effort on unnecessarily intense vigilance at inappropriate times.

**Lidocaine.** Lidocaine is only used parenterally. This drug is very popular in treating acute ventricular arrhythmias where it is usually given as a sudden intravenous injection. If the arrhythmia requires treatment for a few days, constant-rate IV infusion is employed. Intramuscular injections of a special 10% formulation of lidocaine is being studied

by our group and others for possible use against arrhythmias.

**Brief IV injection.** Empirical trial has determined that IV lidocaine doses of 0.5 to 1.5 mg per kg body weight can be repeated every three to five minutes until a 200 to 300 mg dose is reached. This method is usually safe. The time course of plasma lidocaine after an IV injection is shown in figure 2. Several features of interest can be noted. First, the lidocaine concentration rapidly drops below the MEC (15–40 minutes), and the arrhythmia being treated may return. The early rapid drop ( $t_{1/2} = 9$  minutes) in concentration is due to distribution of the drug into its large apparent volume of distribution ( $V_D = 120$  liters). After distribution, the rate of elimination slows and is accomplished by a combination of renal excretion and hepatic metabolism. The hepatic metabolism of lidocaine is so rapid that under ordinary circumstances, less than 5 to 10% of lidocaine is excreted unchanged by the kidney. A note of caution about repeated IV injections or injections during infusions: the volume of distribution is partially filled with drug under these circumstances, and an unexpectedly large increase in plasma concentration may occur.

**Intravenous constant-rate infusion.** This mode of therapy is commonly used. Figure 2 shows the time course of the rise in plasma lidocaine when infusion is begun without prior doses. Because the MEC for lidocaine is usually so low (1 to 2  $\mu\text{g}$  per ml) and the elimination  $t_{1/2}$  so short (1.5 to 2 hours), the plasma concentration usually rises to MEC within an hour. If elimination of lidocaine is normal, a simple, empirical rule can be applied to estimate the plasma lidocaine concentration at steady state—the infusion rate of lidocaine in  $\mu\text{g}$  per minute per kg body weight divided by 10 equals the plasma concentration of lidocaine in  $\mu\text{g}$  per ml, for example, an infusion of 30  $\mu\text{g}$  per minute per kg body weight should produce a plasma concentration of 3.0  $\mu\text{g}$  per ml at steady state. Like any drug with first order kinetics, 90% of the steady state value is achieved in 3.3 times the  $t_{1/2}$ . Most commonly, lidocaine infusions are given following one or more IV injections as shown in figure 3. Since the elimination  $t_{1/2}$  of lidocaine is fairly brief, plasma lidocaine changes fairly rapidly to a new steady state when IV infusion rate is increased or decreased and falls rapidly when an infusion is discontinued. Low cardiac output is associated with reduced hepatic blood flow and a

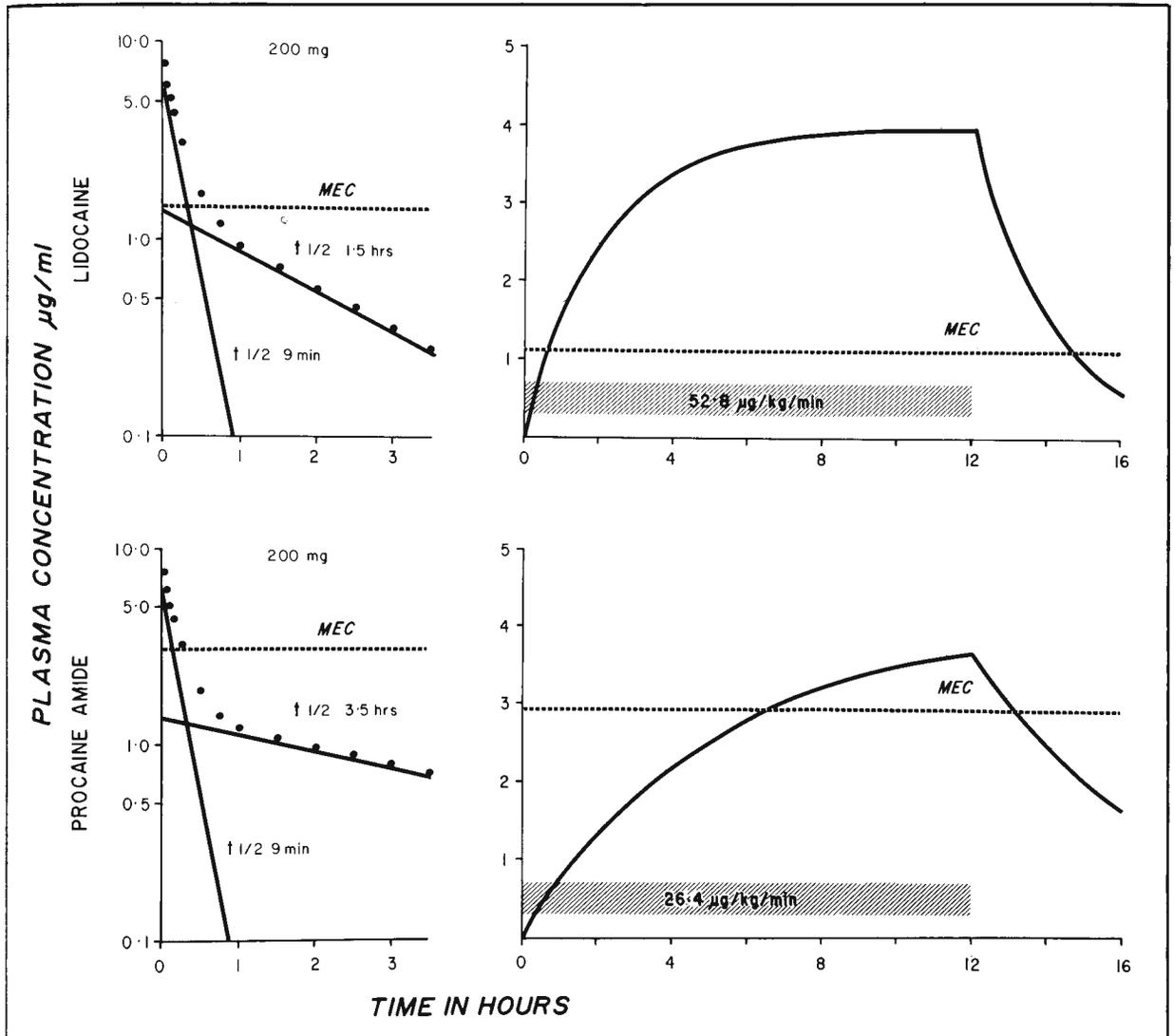


Fig. 2—Time-plasma concentration course of lidocaine and procainamide produced by sudden 200 mg intravenous injection (left) and constant-rate intravenous infusion (right).

After IV injection of either drug (left), the early, rapid fall in plasma drug concentration is due to distribution of drug into its large apparent volume of distribution ( $V_D$ ). A slower late phase of disappearance is seen which is due to elimination of the drugs by a combination of hepatic metabolism and renal excretion. The half-time for elimination ( $t_{1/2e}$ ) is 1.5 hours for lidocaine and 3.5 hours for procainamide.

At right, the plasma concentration during and after a 12-hour constant infusion of procainamide and lidocaine into a 70 kg patient. The infusion rate was selected so that after an infinite amount of time, the plasma concentration of each drug would be 4  $\mu\text{g}/\text{ml}$ . For lidocaine,  $t_{1/2e} = 1.5$  hours,  $V_D = 120$  liters, and infusion rate = 52.8  $\mu\text{g}/\text{min}/\text{kg}$  body weight. For procainamide,  $t_{1/2e} = 3.5$  hours,  $V_D = 140$  liters, and infusion rate = 26.4  $\mu\text{g}/\text{min}/\text{kg}$  body weight. Primarily due to its longer elimination half-life, a much slower rate of procainamide infusion is required to produce a 4  $\mu\text{g}/\text{ml}$  steady-state plasma concentration. Because of its longer  $t_{1/2e}$ , procainamide takes longer to achieve 90% of its steady-state plasma concentration (11.6 hours) than lidocaine (5.0 hours). Also, the plasma concentration of procainamide falls slower after discontinuing the infusion.

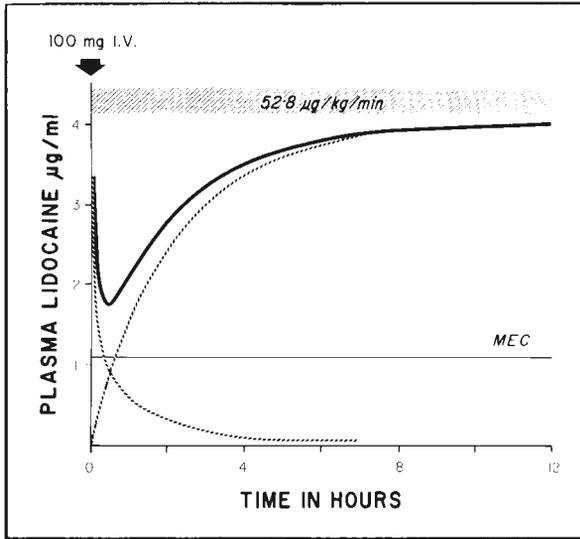


Fig. 3—Combined lidocaine dosage in a 70 kg patient with an initial IV injection of 100 mg followed immediately by an infusion of 52.8  $\mu\text{g}/\text{min}/\text{kg}$  body weight. The *thin solid line* shows the minimum effective concentration (MEC) for antiarrhythmic action. The *thick solid line* shows the concentration-time course resulting from combined therapy. The *two interrupted lines* show the concentration-time course which would have resulted from either mode of dosing alone. Note that this method maintains the plasma concentration in the effective range.

reduced rate of lidocaine elimination. Also, lidocaine elimination can be reduced when hepatocellular function is severely impaired. When congestive failure or another condition reducing metabolism of the drug is present, infusion rates must be reduced accordingly—sometimes by as much as two or three-fold.

**Intramuscular injection.** This route of administration is still being studied for its therapeutic usefulness. The plasma concentration achieved after intramuscular injection seems to depend on the formulation and concentration injected, the particular muscle used for injection, activity in the muscle after injection, and general circulatory status. Using a special 10% solution and a 4 mg per kg body weight given in the deltoid muscle, we usually achieve a 1  $\mu\text{g}$  per ml plasma concentration by 5 minutes, an average peak level of 3.3  $\mu\text{g}$  per ml at 15 minutes, and the concentration exceeds 1  $\mu\text{g}$  per ml for 90 to 120 minutes (fig. 4).

**Oral doses.** When lidocaine is given orally, it is well absorbed, but this route of administration has at least two disadvantages which severely limit

its usefulness. First, the liver metabolizes an incredible proportion of an oral dose when the drug is presented to the liver via the portal circulation, and very low plasma concentrations of lidocaine are achieved. Second, oral doses tend to produce significant abdominal discomfort and, very frequently, nausea. There is evidence to suggest that the nausea may be caused by the central action of a metabolite rather than local gastrointestinal irritation.

**Procainamide.** Procainamide is a more versatile drug than lidocaine not only because of its broader antiarrhythmic spectrum but also because it can be administered by more routes, including the oral route which permits long-term therapy.

**IV injection.** There is a great deal of conflicting data in the literature regarding IV injection of procainamide. Many reports would lead one to believe that precipitous arterial hypotension is almost the rule after IV procainamide. This is true if large injections are given. We have devised a simple method of IV injection which allows rapid control of ventricular rhythms but circumvents hypotension. We give 100 mg IV every five minutes. This leads to a linear rise in plasma drug concentration and progressive decrease in VPD's until they finally disappear. This usually takes 4 to 8 doses and is not accompanied by clinically significant hypotension (fig. 5). Another advantage is that the physician knows immediately whether or not a par-

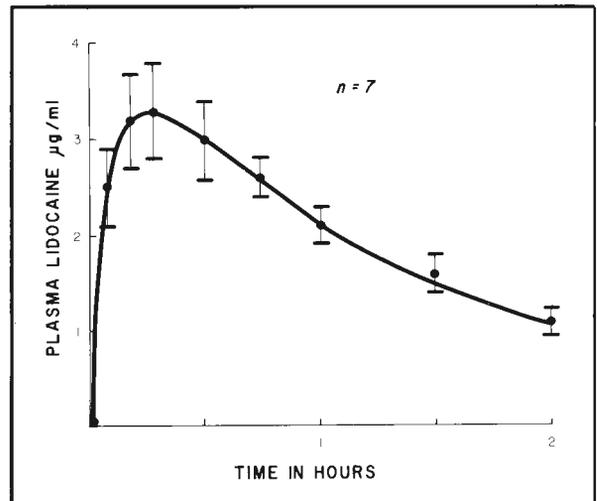


Fig. 4—Average plasma lidocaine as a function of time in seven patients with acute myocardial infarction. Four mg/kg body weight of 10% lidocaine was injected in the deltoid muscle of seven patients during the initial eight hours of acute myocardial infarction.

ticular arrhythmia will respond to this agent and whether high or low concentrations will be required. Like lidocaine, procainamide plasma concentration falls rapidly after a single IV injection because of an initial rapid distribution of the drug into a large apparent volume (fig. 2). The late phase of decline in plasma concentration is due to elimination and has an average  $t_{1/2}$  of 3.5 hours. A large proportion of procainamide is excreted unchanged into the urine (about 60%), but a significant amount is acetylated, presumably by the liver (25-30%).

**Intravenous constant-rate infusion.** We have used this method for many years, particularly in the intensive care unit when a stable plasma concentration is desired. Figure 2 shows the plasma concentration of procainamide during and after an IV infusion. Because the MEC of procainamide is higher than lidocaine and the elimination  $t_{1/2}$  is longer ( $\pm 3.5$  hours), infusions may not yield therapeutic concentrations until about 6 hours have elapsed, and 90% of steady-state concentration is reached at 12 hours ( $3.3 \times 3.5$ ). Because the elimination  $t_{1/2}$  of procainamide is about twice as long as that of lidocaine, the former drug takes longer to achieve a new steady state after a change in infusion rate and falls much slower when an infusion is stopped. Figure 4 shows the combination of intermittent IV injection therapy with constant-rate infusion.

**Intramuscular injection.** Procainamide is fairly well absorbed after IM injection and when given by this route rapidly produces antiarrhythmic plasma concentrations which decline as expected from its elimination  $t_{1/2}$ . The rate at which a MEC is achieved is not a great deal faster than after an oral dose. Therefore, unless the patient is unable to take the drug by mouth, there is little indication for IM administration.

**Oral doses.** Procainamide can be given by mouth which is a major advantage over lidocaine. The drug is not well absorbed from the stomach when the pH is acid, and delay in gastric emptying can cause a delay in onset of absorption. However, this drug is quickly absorbed from the alkaline small intestine; after adequate doses, effective plasma levels are achieved in 15 minutes or so, and the peak level is achieved between 45 and 75 minutes after a dose. Absorption is virtually complete after 90 to 105 minutes, and elimination takes place with a  $t_{1/2}$  of 3.5 to 4 hours. Renal excretion of procainamide is greatly reduced when the urine is alkaline,

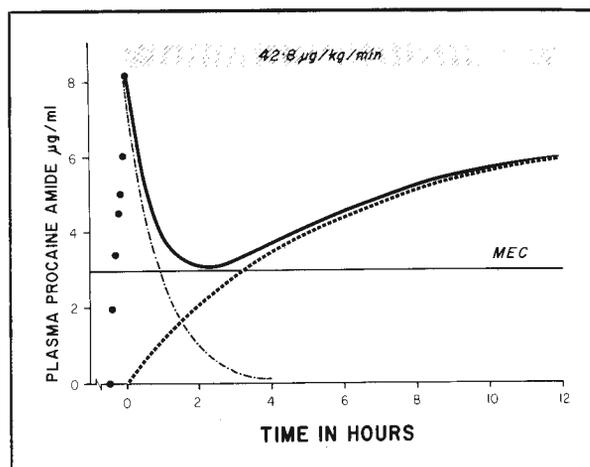


Fig. 5—Plasma procainamide concentration plotted as a function of time when drug is given by incremental intravenous dosing and/or constant intravenous infusion. The minimum effective concentration, MEC, is represented by the thin solid line. Six 100 mg doses of procainamide are given every 5 minutes, black dots, until the arrhythmia is completely suppressed at a plasma drug concentration of 8.2  $\mu\text{g/ml}$  within 30 minutes. The dash-dot line shows the concentration-time course which would have resulted if incremental doses were stopped and no other mode of dosing started. Without prior injection, when a constant intravenous procainamide infusion (42.8  $\mu\text{g/min/kg}$  body weight) is started, dashed curve, the plasma drug concentration would be above the MEC at 3 hours and is 6.5  $\mu\text{g/ml}$  at steady state. The thick black line represents the plasma procainamide concentration which would be obtained by initially giving the six 100 mg injections and, then, immediately beginning a constant IV infusion of 42.8  $\mu\text{g/min/kg}$  body weight. Note that the procainamide concentration never falls below the MEC.

and in instances of congestive failure or renal failure. In these situations, a larger proportion of a given dose is acetylated by the liver. In congestive failure, procainamide, like lidocaine, has a smaller apparent volume of distribution, which means the same amount of drug in the body will result in a higher plasma drug concentration. Some years ago we noted procainamide toxicity occurring during the change from intravenous constant-rate infusions of procainamide to an oral regimen, even though the total 24-hour doses were identical. Our error is shown in figure 6 (upper panel). Since an oral dose produces a rapid rise in plasma concentration, an initial oral dose given immediately on stopping the infusion causes a high (toxic) plasma concentration. It is apparent that an oral dose of a rapidly absorbed drug is tantamount to an IV injection. This unfor-

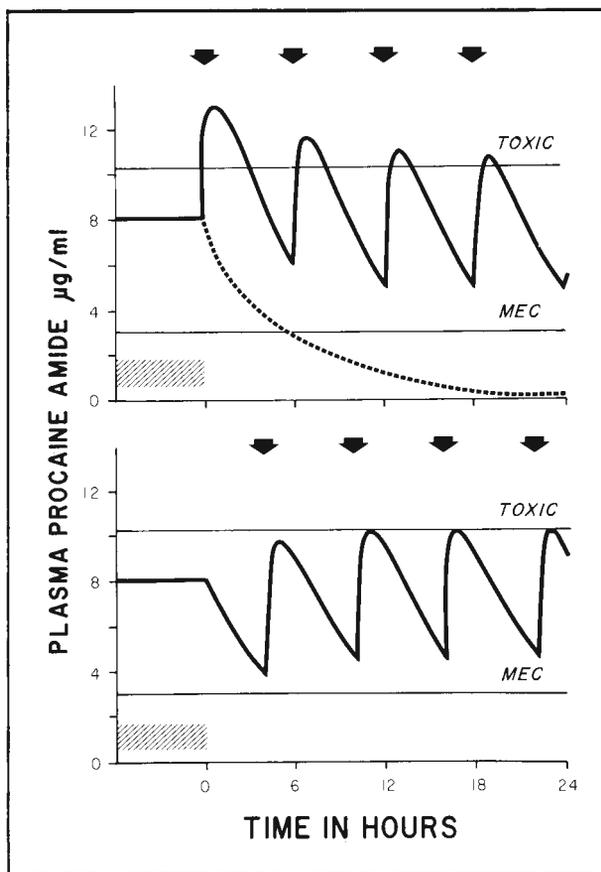


Fig. 6—Changing from continuous intravenous infusion to an oral dose regimen of procainamide  $V_D = 140$  liters,  $t_{1/2e} = 4.0$  hours.

The upper graph shows the termination of an intravenous infusion which for three days had maintained a stable plasma procainamide concentration of  $8 \mu\text{g/ml}$ . At time = 0, the infusion was discontinued and a regimen of 1,000 mg oral doses every 6 hours was begun. Note that toxic concentrations are obtained after each of the first four oral doses although this will ultimately be a satisfactory regimen at steady state.

The lower graph shows an identical patient, given an identical infusion and oral dosage regimen with only one exception—four hours were allowed to elapse between cessation of infusion and beginning the oral drug. Note that the plasma procainamide concentration never reaches toxic concentrations.

tunate sequence can be avoided completely by waiting for about four hours after discontinuing the infusion before giving the first oral dose (fig. 6, lower panel).

**Toxicity.** While antiarrhythmic drugs have considerably decreased mortality from arrhythmias seen following acute myocardial infarction and open heart surgery, improper use of these agents is as

potentially life-threatening as the presence of the arrhythmia itself. A considerable incidence of toxicity is still encountered in using these drugs and impairs their general usefulness. Toxicity usually results from insufficient attention to the general physiologic state of the patient, the functional impairment of the organs which metabolize these drugs, or pharmacodynamic considerations. However, even when errors in judgement are made using these drugs, a thorough knowledge of their toxic effects and a continuing careful search for early toxic signs can often prevent more severe and serious toxicity.

**Lidocaine.** Clinical toxicity of lidocaine appears to be related to size of dose and rate of administration. Ordinary doses, however, may produce undesirable effects when there is severe hepatic disorder, acidosis, severe congestive heart failure, low cardiac output, and shock. If lidocaine is infused at usual rates where these conditions exist, toxicity may ensue and, in fact, where blood levels have been measured in these cases, they are frequently two or three times higher than those needed for effective therapy.

Lidocaine usually produces signs of central nervous system (CNS) involvement before any subjective or objective cardiovascular effects are observed. The early symptoms may be extremely subtle. Blood levels greater than  $6 \mu\text{g}$  per ml have been associated with dizziness, drowsiness, numbness of lips and tongue, speech disturbances, and psychosis. At present we suspect that many of the minor CNS symptoms of lidocaine toxicity go unrecognized as such and are treated with diazepam or a similar agent. More severe CNS manifestations such as tremor, convulsions, respiratory depression, and areflexia occur most commonly when venous blood levels of lidocaine are higher than  $10 \mu\text{g}$  per ml but may be seen at lower concentrations. Signs of CNS toxicity may be treated by stopping lidocaine infusion and, as a rule, symptoms will improve within 15-30 minutes, but may take several hours to completely abate. Lidocaine-induced convulsions may require treatment with small intravenous doses of short-acting barbiturates. High doses of barbiturate should be avoided since their CNS depressant effects may potentiate those of lidocaine and may result in respiratory arrest.

The hemodynamic effects of 1 mg per kg of lidocaine injected intravenously have been measured by several groups. While hypotension may result

from larger doses of lidocaine, in therapeutic doses, there appears to be little effect on systemic arterial pressure, ventricular contractile force, cardiac output, heart rate, or stroke volume in man. Thus, it would seem that lidocaine given in this way exerts remarkably few if any adverse effects of clinical significance. The hemodynamic effects of lidocaine in the shock state or after a constant intravenous infusion are as yet unknown.

Finally, lidocaine has been suspected of producing cardiovascular toxicity. Clinical observations, largely unsubstantiated by conclusive evidence, have implicated lidocaine as the cause of: 1) rapid ventricular response to an atrial arrhythmia, 2) production of ventricular arrhythmia, or increase in number of ectopic beats, 3) heart block, and 4) asystole. The use of lidocaine is not advised in the presence of heart block.

*Procainamide.* Procainamide is more prone to produce direct cardiac toxicity expressed as alterations in electrical and mechanical behavior of the heart than lidocaine. As with lidocaine, many of the toxic reactions seen with procainamide are related to size of dose and also to the route of administration. Rapid intravenous administration, particularly when given faster than 50-75 mg per minute, has been associated with undesirable electrocardiographic and hemodynamic effects. Because of this, oral and intramuscular use of procainamide has been advocated. However, even with these routes of administration and recommended dose size, toxicity may be encountered in congestive heart failure, renal disease, or shock.

In our experience, therapeutic effectiveness and toxicity of procainamide are closely related to plasma drug concentration. We consider the effective antiarrhythmic plasma drug concentration range to be 3 or 4-10  $\mu\text{g}$  per ml and have observed electrophysiologic and hemodynamic toxicity at concentrations greater than 12  $\mu\text{g}$  per ml. Notwithstanding the bad reputation of intravenously administered procainamide, we have found that antiarrhythmic plasma drug concentrations are attained rapidly, safely, and predictably when procainamide is given intravenously. We recommend 100 mg of procainamide be given intravenously every 5 minutes with electrocardiographic and blood pressure monitoring. An example of this method is shown in figure 4; the electrocardiogram was continuously monitored and patient P.B. was given 100 mg of procainamide every 5 minutes until VPD's were abolished. Plasma

samples taken 4½ minutes after each dose indicate there is a direct linear relationship between cumulative dose and plasma drug concentration. Moreover, after each procainamide injection, the number of VPD's diminishes until the sixth dose when the arrhythmia is completely abolished and a plasma drug concentration within the therapeutic range (8.3  $\mu\text{g}$  per ml) is achieved. Neither untoward hemodynamic nor electrocardiographic effects were encountered during the course of treatment.

Even at low plasma drug concentration range, procainamide produces electrocardiographic changes resulting from its cardiac electrophysiologic actions. The P-R, QRS, and QT intervals are all prolonged at therapeutic plasma concentrations. In addition, toxic drug concentrations have been associated with progression of these or appearance of more dramatic electrophysiologic effects such as: 1) suppression of cardiac automaticity, including the S-A node, leading to asystole, 2) impairment of A-V conduction, leading to heart block, and 3) slowing of intraventricular conduction greater than 30%. Another noteworthy undesirable electrocardiographic change stems from the fact that toxic concentrations of procainamide almost invariably cause increased automaticity and multifocal pacemaker activity in isolated cardiac Purkinje fibers. Thus, the appearance of ectopic ventricular beats, ventricular tachycardia, or fibrillation in a patient who presumably has achieved therapeutic drug concentration may not represent arrhythmia breakthrough but rather procainamide toxicity. If the physician is unaware of this complication, he may continue to administer procainamide or even increase the dose, not realizing that the drug is responsible for evoking the arrhythmia. Since therapeutic and toxic drug effects are so well correlated with electrocardiographic changes, the electrocardiogram is an excellent way to monitor procainamide efficacy and, when carefully used, the incidence of toxicity is likely to be reduced. Because of its depressant effects on A-V conduction and ventricular automaticity, procainamide is contraindicated in heart block, and cautious use has been advised in patients with wide QRS intervals and bundle branch block.

Procainamide may produce hemodynamic changes by depressing myocardial contractility and the cardiac output and thereby produce hypotension. While the severity of these hemodynamic alterations appears to be related to dose size and rate of administration, they may be further intensified by heart

disease and congestive heart failure. Although procainamide should be used cautiously in these conditions, they do not preclude therapy. We have noted that the probability of untoward hemodynamic effects is minimized by intermittent intravenous injections and by careful monitoring of blood pressure. If necessary, doses higher than 1000 mg may be given by this technique without evidence of cardiac toxicity or hypotension. Procainamide-induced hemodynamic or electrocardiographic toxicity may be treated by molar sodium lactate and the catecholamines, norepinephrine or isoproterenol.

Extracardiac toxic reactions to procainamide are most commonly seen during chronic oral therapy. Gastrointestinal disturbances (nausea, vomiting, diarrhea), and CNS disturbances (mental depression, psychosis, and convulsions) have been reported. Other toxic effects include skin rash, fever and chills, and agranulocytosis. Most of these extracardiac reactions subside almost immediately with

discontinuation of the drug, but some may persist a few days to a few weeks. A syndrome resembling systemic lupus erythematosus (SLE) characterized by arthralgia, fever, pleuropneumonic involvement, and hepatomegaly has occurred frequently in patients on long-term maintenance therapy. Rarely, adrenal corticosteroids have been required to control unusually tenacious symptoms of SLE. It should be pointed out that, unlike SLE, the drug induced SLE-like syndrome produces no permanent damage in any vital organ system. This and the fact that aspirin or steroids may control symptoms are important considerations in planning the management of a patient who has a life-threatening arrhythmia for which other drugs are ineffective, and who has developed the SLE-like syndrome. In such a case, one reasonable course of action is to continue procainamide and control symptoms of the SLE syndrome with salicylates or adrenal corticosteroids.