The Antiarrhythmic Properties of Lidocaine and Procaine Amide

Clinical and Physiologic Studies of Their Cardiovascular Effects in Man

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The operative management of patients with congenital or acquired heart disease is often complicated by the occurrence of ventricular arrhythmias. Bigeminal rhythm or premature ventricular contractions are frequently noted with the induction of anesthesia, with tracheal intubation, during dissection and manipulation of the heart and great vessels, and with nasotracheal aspiration in the postoperative period. Their initial occurrence is most often related to a temporary period of hypoxia, but in many patients, particularly those with advanced myocardial disease accompanying an acquired valvular lesion, premature contractions may persist or progress to sustained ventricular tachycardia even after the precipitating hypoxia has been corrected. Under these circumstances, the administration of an effective antiarrhythmic agent is indicated, not only to restore a normal rhythm, but, more importantly, to prevent progression of the abnormality to ventricular fibrillation.

In the past, procaine and the longer-acting related compound, procaine amide, have been most widely employed for the treatment of the various ventricular arrhythmias occurring in the course of cardiac operations.1-3 These compounds, however, cause significant systemic hypotension3-5 and this side effect frequently precludes the administration of a therapeutically effective dose. In addition, both procaine and procaine amide have been shown experimentally to impair myocardial contractile force and to lower cardiac output and systemic arterial pressure.3,4,6 In 1950 Southworth and his collaborators7 presented the first clinical evidence that another local anesthetic agent, lidocaine (Xylocaine), had an antiarrhythmic effect. Since that time this property of lidocaine has been confirmed by several experimental studies and clinical reports,8-11 which indicated that it might be preferable to procaine amide in the management of ventricular arrhythmia. In the present study the effects of lidocaine and procaine amide on arterial pressure, heart rate, myocardial contractile force, and ventricular excitability were determined in 12 patients. These physiologic observations and clinical experiences in the treatment of ventricular arrhythmias with lidocaine are described.

Methods

Physiologic studies were performed in 12 patients undergoing corrective cardiac operations. The patients ranged in age from 6 to 48 years; their cardiovascular anomalies were atrial septal defect (five patients); ventricular septal defect (three patients); valvular pulmonic stenosis (three patients); and acquired aortic stenosis (one patient). All patients were receiving maintenance doses of digoxin at the time of study and all were in normal sinus rhythm. After preanesthetic medication, anesthesia was induced with sodium thiopental or halothane and was maintained with nitrous oxide, oxygen, and halothane in a concentration of 0.5 to 1.0 per cent. Systemic arterial pressure was recorded from a catheter in the radial artery. After the heart had been exposed, a bipolar stimulating electrode8 and a Walton-Brodie strain-gage arch12 were sutured to the right ventricle. The signal from the arch was recorded with the arterial pressure pulse and electrocardiogram on a multi-channel oscillograph. Ventricular excitability was assessed by delivering electrical stimuli of 2-msec. duration to the heart at various

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*The electrode used was the University of Minnesota temporary pacemaker electrode manufactured by the Medtronic Corp., Minneapolis.
times during the cardiac cycle. The stimulator was triggered from the R wave of the electrocardiogram through a variable time-delay circuit. By relating the amplitude of threshold stimulation current to the interval after depolarization, stimulus strength-interval curves were constructed that defined the absolute refractory period and the period of maximum excitability during diastole. In five of the 12 patients studied, two or more stimulus strength-interval curves were inscribed and the diastolic stimulation threshold was found to vary by no more than ±0.1 milliamper. The absolute refractory period of the ventricle is not expressed as an absolute value, but as a percentage of the cycle length, since this percentage has been shown to remain the same at various heart rates. The relative refractory period was not precisely defined, since this measurement requires many additional threshold determinations, and these were found to prolong the period of study beyond safe and reasonable limits.

After control observations of the above variables, either lidocaine (1.0 mg./Kg.) or procaine amide (2.0 mg./Kg.) was given as a single intravenous injection. Arterial pressure and myocardial contractile force were continuously recorded and 5 minutes after the drug had been injected a second stimulus strength-interval curve was determined. In nine patients a second and larger dose of the same drug (lidocaine 2.0 mg./Kg. or procaine amide 4.0 mg./Kg.) was given 15 minutes after the initial one, and 5 minutes later a third stimulus strength-interval curve was inscribed.

In the 6-month period in which the above physiologic studies were being carried out, lidocaine was employed for the treatment of ventricular arrhythmia in 28 patients during or following intracardiac operations; 24 of the patients were adults with acquired aortic or mitral valve disease. In every instance the course of the arrhythmia was documented electrocardiographically before and at intervals after lidocaine was administered intravenously.

**Results**

**Hemodynamic Studies**

The effects of lidocaine and procaine amide on systemic arterial systolic pressure and on myocardial contractile force were determined in 10 of the 12 patients and the maximal variations from control values are shown in figures 1 and 2. Lidocaine in a dose of 1.0 mg./Kg. resulted in an increase in systolic pressure in every patient, but after 2.0 mg./Kg. the pressure fell in four of the five patients. These changes in systolic arterial pressure were of small magnitude, however, the maximum increase over the control level being 7 mm. Hg and the greatest decrease 9 mm. Hg. The systolic arterial pressure fell in every patient given procaine amide, either 2.0 or 4.0 mg./Kg. In four patients only moderate decreases ranging from 7 to 19 mm. Hg followed the larger dose, but marked hypotension occurred in one patient with an atrial septal defect after only 2.0 mg./Kg.
Right ventricular contractile force changed only slightly after the administration of either dose of lidocaine; small increases in amplitude occurred in four of five patients after 1.0 mg./Kg., but decreases to below control levels were noted in two of them after they were given 2.0 mg./Kg. (fig. 2). Procaine amide resulted in more marked reductions in contractile force. The average decrease was 14 per cent after 2.0 mg./Kg. and 21 per cent after 4.0 mg./Kg.

There was no systematic or significant change in heart rate following the administration of either drug; the maximum increase in rate was 12 beats per minute and the maximum decrease was 7 beats per minute. No alteration in the configuration or duration of the QRS complex occurred in any patient after either lidocaine or procaine amide.

**Ventricular Excitability**

The changes in diastolic threshold that occurred after the administration of lidocaine and procaine amide are illustrated in figure 3. The current required to produce a ventricular premature contraction during diastole was increased from an average of 1.1 milliamperes to 1.4 milliamperes 5 minutes after the administration of 1 mg./Kg. lidocaine, and to 1.9 milliamperes 5 minutes after 2 mg./Kg. of lidocaine were given. The significance of these changes in the diastolic threshold following lidocaine administration is indicated by p values of <0.01 and <0.02 for the smaller and larger doses, respectively. The diastolic threshold to ventricular stimulation also increased after procaine amide was given. The average control current was 1.2 milliamperes; it rose to 1.5 milliamperes following 2.0 mg./Kg. procaine amide and to 1.7 milliamperes after 4.0 mg./Kg. The changes in the diastolic threshold to stimulation with procaine amide were significant at the 4.0 mg./Kg. dose (p < 0.01) but the changes with the smaller dose were not significantly different from control (p > 0.10).

The changes in the relative duration of the absolute refractory period noted after the administration of lidocaine and procaine amide are shown in figure 4. As noted above, the changes are expressed as fractions of the R-R interval to compensate for the small changes in heart rate that occurred in some patients. Neither drug caused a significant alteration in the duration of the absolute refractory period; the maximum increase and decrease were +5 and -2 per cent of the cycle length, respectively. In the seven patients given lidocaine, the actual duration of the absolute refractory period averaged 244 msec. during the control period and increased to averages of 253 and 264 msec. after 1.0 mg./Kg. and 2.0 mg./Kg. of the compound were administered. In the five patients to whom procaine amide was given, the absolute refractory period averaged 222 msec. in the control period, 238 msec. after 2.0 mg./Kg., and 255 msec. after 4.0 mg./Kg.

**Clinical Observations**

Twenty-eight patients with ventricular arrhythmias, occurring during or following cardiac operations, were treated with lidocaine.
LIDOCAINE AND PROCAINE AMIDE

Figure 5
Electrocardiograms, recorded in the immediate postoperative period, of a patient in whom prosthetic replacement of both the mitral and tricuspid valves had been carried out. Before treatment (above) bigeminal rhythm and multiple premature ventricular contractions are evident. Two minutes after 100 mg. of lidocaine were administered intravenously the basic rhythm of atrial fibrillation had been restored. In this instance the duration of the lidocaine effect was 12 minutes.

 Twelve had frequent ventricular premature contractions and following a single or repeated intravenous dose of 50 mg. the basic rhythm, either sinus or atrial fibrillation, was restored in 11 of them. Bigeminal rhythm was present in nine patients and conversion to basic rhythm occurred in every patient after either 50 or 100 mg. of lidocaine were given (fig. 5). Seven patients had sustained ventricular tachycardia; in each of them 100 mg. of lidocaine was employed as the initial dose; one patient received 500 mg. over a 30-minute period. Six of these patients reverted to their basic rhythm after lidocaine; one exception was a patient with aortic stenosis in whom ventricular tachycardia persisted after 250 mg. of lidocaine followed by 3.5 Gm. of procaine amide.

In the total group of 28 patients the ventricular arrhythmia was permanently abolished by lidocaine in only six. In the other patients the duration of the antiarrhythmic effect of lidocaine was 10 to 20 minutes, after which time bigeminal rhythm or persistent extrasystoles were again noted. In many of these patients additional doses of lidocaine were given periodically until the circulatory or ventilatory factors basically responsible for arrhythmia had been corrected and the drug was no longer necessary. Ventricular tachycardia did not recur in any of the six patients who responded to lidocaine. None of the 28 patients treated with lidocaine demonstrated a significant decrease in blood pressure after the agent was administered.

Discussion
The effectiveness of lidocaine in controlling ventricular arrhythmias is demonstrated by the response of the patients described above, and this clinical experience confirms the previous observations reported by Hitchcock and Keown and Weiss. Before the present authors were familiar with the antiarrhythmic properties of lidocaine, procaine and procaine amide were the only drugs used in the clinic to treat patients who developed ventricular arrhythmias during operation. These agents caused hypotension so often, however, that they were given with the greatest reluctance and frequently only after sustained ventricular tachycardia had developed. Even in this situation, electric shock was often considered preferable. Because of the information fur-
nished by the clinical and physiologic studies described above, however, lidocaine is administered without hesitation and, in many instances, is even given prophylactically. In a patient severely ill with aortic stenosis or regurgitation, for example, 50 mg. of lidocaine may be injected before the induction of anesthesia and this dose repeated a few minutes before tracheal intubation. When frequent premature contractions occur during the operation, lidocaine is immediately given but concurrently the patient’s ventilation and oxygenation are assessed by rapid determinations of the pO₂ and oxygen saturation of arterial blood. If these values are found to be abnormally low, ventilation must be increased until adequate oxygenation is restored. If arrhythmia recurs or persists in the absence of demonstrable hypoxia, repeated doses of lidocaine are given whenever necessary. The total permissible dose of lidocaine in an anesthetized patient has not been established, but one of our adult patients was given 500 mg. within a 1-hour period without detectable signs of toxicity.

The duration of the antiarrhythmic effect of lidocaine is relatively brief, 10 to 20 minutes. This property of the drug makes it particularly suitable for use in surgical patients, since, as noted above, arrhythmia in the operative or postoperative period is usually precipitated by some acute stimulus ordinarily amenable to correction. Lidocaine has been found similarly useful in the course of cardiac catheterization and selective angiocardiography. The drug will often terminate a ventricular arrhythmia induced by the catheter and allow completion of an important study. It may be used prophylactically when ventricular irritability is present before the study is begun.

The electrophysiologic studies described above indicate that, in the doses employed, both lidocaine and procaine amide cause an elevation in the electrical stimulation threshold of the ventricle during diastole, and it would appear that this effect may be related to their antiarrhythmic actions. No significant change in the duration of the absolute refractory period occurred with either drug in any patient. These effects of procaine amide are in agreement with the experimental work of Woske et al., who demonstrated that procaine amide raised the diastolic stimulation threshold but did not significantly prolong the refractory period of the ventricle. With respect to lidocaine, however, the present observations are in contrast to those of Hitchcock and Keown, who reported that, in animals, unspecified doses of lidocaine greatly altered the refractory period as well as the conduction and “depolarization” times.

The doses of lidocaine and procaine amide employed in the present studies were chosen because they were considered comparable to those which have been shown to be effective in the clinical treatment of ventricular arrhythmia. Both compounds were found to decrease the susceptibility of the ventricle to electrical stimulation, but lidocaine must be considered the more effective agent, since smaller doses of it were required to elevate the diastolic threshold and significant depression of arterial pressure and myocardial contractile force did not occur after its administration. Although hypotension may result from larger doses of lidocaine, experimental studies in both man and in animals have shown that doses similar to those given to these patients cause no circulatory depression. In contrast, the depressive effects of procaine and procaine amide on the circulation are well known to all physicians who have employed these drugs in the treatment of arrhythmias, and they have also been documented experimentally in animals and in man. Every patient in the present study, for example, who was given procaine amide, either 2.0 or 4.0 mg./Kg., evidenced a fall in arterial pressure and a decrease in the contractile force of the right ventricle.

The physiologic observations on which this report is based were, of course, made in patients who had congenital or acquired heart disease severe enough to necessitate an open corrective operation and in whom the regulatory mechanisms of the circulation may have been altered or impaired by the circumstances.
of the operation and the anesthetic state. These, however, are the types of patients and the circumstances in which ventricular arrhythmias most often occur and in which treatment may be life-saving. In therapeutically effective doses, lidocaine was found to decrease ventricular excitability and to have no adverse effects on the circulation. It is concluded, therefore, that lidocaine is the drug of preference for the treatment of ventricular arrhythmia in patients undergoing cardiac operations.

Summary
The effects of lidocaine (Xylocaine) and procaine amide on arterial pressure, myocardial contractile force, and ventricular excitability were studied in 12 patients undergoing cardiac operations. Both compounds resulted in an increase in the stimulation threshold of the ventricle during diastole and neither caused a significant change in the duration of the absolute refractory period. Lidocaine, in doses of 1.0 to 2.0 mg./Kg., produced no significant circulatory depression but every patient given procaine amide (2.0 or 4.0 mg./Kg.) evidenced a fall in arterial pressure and a decrease in the contractile force of the right ventricle. These physiologic observations and clinical experiences with the use of lidocaine indicate that it is an effective antiarrhythmic agent and that it is preferable to procaine amide in the management of ventricular arrhythmias that occur during and following cardiac operations.

References
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Circulation. 1963;28:486-491
doi: 10.1161/01.CIR.28.4.486
Circulation is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 1963 American Heart Association, Inc. All rights reserved.
Print ISSN: 0009-7322. Online ISSN: 1524-4539

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://circ.ahajournals.org/content/28/4/486

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