Effects of Procainamide and Lidocaine on Electrically Inducible Ventricular Tachycardia Studied with Programmed Ventricular Stimulation in Post Myocardial Infarction

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The effects of procainamide and lidocaine, representative of class IA and IB antiarrhythmic agents, on electrically inducible ventricular tachycardia (VT) were studied using programmed ventricular stimulation in 47 post myocardial infarction patients at an average of 1.5 months after the onset. The mean doses of administered procainamide and lidocaine were 1050 mg and 161 mg, and their mean plasma concentrations were 7.5 $\mu\text{g/ml}$ and 3.1 $\mu\text{g/ml}$ respectively. The induction of sustained VT was suppressed in 15 of 29 patients (52%) by procainamide, but in none by lidocaine. The induction of nonsustained VT was suppressed in 6 of 18 patients (33%) by procainamide, and in 1 of 8 patients (13%) by lidocaine. The efficacy rate of procainamide was significantly higher than that of lidocaine in suppression of VT induction (21/47 vs 1/14 $p < 0.01$). Procainamide significantly prolonged the effective refractory period of the right ventricle as well as the HV and QRS interval, however lidocaine did not affect them significantly. On the other hand, the worsening effect which changed nonsustained VT inducible in the baseline into sustained VT inducible post drug administration was demonstrated in 8 of 18 procainamide cases (44%), and in 3 of 8 lidocaine cases (38%). Between the procainamide effective and ineffective or worsening patients, there were no differences found in the electrophysiologic variables either in the baseline or post procainamide administration.

We concluded that procainamide was more effective than lidocaine for the prevention of potential life-threatening VT induction in post myocardial infarction patients, although its efficacy was considerably limited, and to confirm the effectiveness and exclude the worsening effects of the class IA and IB antiarrhythmic agents, drug testing using programmed ventricular stimulation appeared to be valuable.

Key words:

Antiarrhythmic effect
Proarrhythmic effect
Electrically inducible ventricular tachycardia
Programmed ventricular stimulation
Post myocardial infarction

THE risk of sudden cardiac death is high in survivors of acute myocardial infarction, and its major cause has been indicated to be life-threatening ventricular tachyarrhythmias.¹⁻⁴ Frequent and repetitive ventricular premature complexes detected by ambulatory electrocardiographic monitoring and left ventricular

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dysfunction have been reported to be predictors of increased mortality.⁴⁻⁷ However the predictive accuracy of these markers of the risk for sudden death is not necessarily high, and their interpretation is still somewhat controversial in the literature.⁴⁻⁷

Recently, programmed ventricular stimulation of the heart has been used to identify patients at high risk of sudden cardiac death or spontaneous development of ventricular tachycardia following myocardial infarction.⁸⁻²⁰ This is based on the idea that sudden cardiac death after acute myocardial infarction is caused, in the majority of cases, by spontaneous occurrence of sustained ventricular tachycardia or fibrillation and that programmed ventricular stimulation is effective in disclosing the substrate which initiates and perpetuates those reentrant sustained ventricular tachyarrhythmias with or without clinical documentations of spontaneously occurring arrhythmias.⁸⁻²⁰ Programmed ventricular stimulation was initially used in the diagnosis and management of recurrent sustained ventricular tachycardia. The usefulness of this technique in evaluating the efficacy of antiarrhythmic agents on electrically inducible ventricular tachycardia has also been well appreciated.²¹⁻²³

In this study using programmed ventricular stimulation, we investigated the effects of the most widely used class IA and IB antiarrhythmic agents on electrically inducible ventricular tachycardias in potential high risk patients of post myocardial infarction. We aimed to evaluate the efficacy and limitations of treatment with conventional antiarrhythmic agents in preventing sudden cardiac death and life-threatening ventricular tachyarrhythmias. We also studied the utility of drug testing using programmed ventricular stimulation.

METHODS

The subjects in this study were 47 patients (42 males and 5 females) associated with ventricular tachycardia (VT) induced by programmed ventricular stimulation. Programmed ventricular stimulation was performed in 120 patients at an average of 1.5 months (1-6 months) after acute myocardial infarction in an attempt to identify high risk patients for sudden cardiac death. The mean age was 53 years, and mean left ventricular ejection fraction was $51 \pm 14\%$ (mean $\pm$ SD).

Informed consent was obtained following an explanation of the significance and risks of VT

induction study. Then patients underwent baseline electrophysiologic study in the fasting state under light diazepam sedation. All the antiarrhythmic agents were discontinued at least 5 half-lives in the plasma before study. Following standard electrophysiologic technique, 2 quadripolar electrode catheters were inserted percutaneously through a femoral vein and positioned at the right ventricular apex and outflow tract to stimulate the heart and record local endocardial electrograms. Another catheter was placed at the His region for recording the His-bundle electrogram or at the high right atrium for atrioventricular sequential pacing. Electrocardiographic leads I, II and V1, and 5 traces of intracardiac electrograms recorded at the right ventricular apex, outflow tract, His region or high right atrium were displayed on an oscilloscope and recorded with an ink-jet recorder (Siemens-Elema Mingograf 82) at a paper speed of 50 or 100 mm/sec. All these records were stored on magnetic tape by a data recorder. Cardiac stimulation was performed with rectangular pulses of 1 ms duration at a stimulus strength of twice diastolic threshold using a programmable stimulator (FUKUDA Cardiac Stimulator BC-02).

The programmed ventricular stimulation was performed with 2 basic drive cycle lengths (400 and 600 ms) of 5 beats followed by extrastimuli. Single and then double extrastimuli were introduced from the right ventricular apex and outflow tract. If sustained VT was not induced, triple extrastimuli were introduced from both right ventricular sites. The end point of stimulation protocol was the induction of sustained VT or completion of the protocol.

After the completion of the baseline study, the drug effect was tested in the patients with VT inducible using the same stimulation protocol after the application of the drug. Procainamide was administered intravenously at a rate of 50 mg/min up to a total dose of 1-2 g. Lidocaine was administered intravenously at a dose of 2-3 mg/kg and a rate of 30 mg/min, followed by a continuous infusion at a rate of 1-3 mg/min. In 34 cases, either procainamide or lidocaine was tested. The combined effects of procainamide and lidocaine were studied in 3 cases when lidocaine was administered immediately after procainamide testing was completed. In the remaining 13 cases lidocaine and then procainamide, which was administered 1 hr after the completion of lidocaine testing, were tested

TABLE I PERTINENT ELECTROPHYSIOLOGIC DATA OF THE INDUCED VENTRICULAR TACHYCARDIA (VT)

	No. of cases	VTCL (ms)	Initiation mode				Termination mode	
			S ₂	S ₂ S ₃	S ₂ S ₃ S ₄	burst VP	burst VP	DC shock
Sustained VT	29	238 ± 66 (mean ± SD)	2	7	19	1	14	15
Polymorphic	4	193 ± 15	0	1	3	0	0	4
Monomorphic	25	245 ± 61	2	6	16	1	14	11
Nonsustained VT	18	235 ± 27	0	3	15	0	spontaneous	
Polymorphic	9	218 ± 26	0	3	6	0	spontaneous	
Monomorphic	9	243 ± 21	0	0	9	0	spontaneous	

VT = ventricular tachycardia; VP = ventricular pacing; DC = direct current; CL = cycle length

TABLE II SUPPRESSIVE EFFECTS OF PROCAINAMIDE AND LIDOCAINE ON VT INDUCTION

Type of VT	Procainamide	Lidocaine	
Sustained VT	15/29 (52%)	0/6 (0%)	$p < 0.024$
Nonsustained VT	6/18 (33%)	1/8 (13%)	$p < 0.027$
Total	21/47 (45%)	1/14 (7%)	$p < 0.011$

VT = ventricular tachycardia

respectively. Plasma concentration of the drug was measured immediately after the testing was completed.

For statistical analysis, paired and unpaired *t* test and Fisher's exact test were used. A *p* value < 0.05 was considered significant. Values are expressed as mean ± standard deviation.

Sustained VT was defined as VT lasting longer than 30 seconds or requiring termination before that period because of hemodynamic compromise. Nonsustained VT was defined as 10 or more consecutive ventricular beats terminating spontaneously in less than 30 seconds. Induced VT was classified into monomorphic VT with constant QRS configuration and axis, and polymorphic VT with changing QRS configuration and axis in successive beats.

The drug effects were judged as effective when nonsustained VT changed into no VT inducible or sustained VT changed into no VT or nonsustained VT inducible after the drug administration. A worsening effect of the drugs was defined as nonsustained VT changed into sustained VT inducible.

RESULTS

The pertinent data on induced VT at baseline

programmed ventricular stimulation are shown in Table I. Forty seven VTs consisted of 25 sustained monomorphic, 4 sustained polymorphic, 9 nonsustained monomorphic and 9 nonsustained polymorphic VT. The mean cycle lengths of induced VT were 238 ± 66 ms in sustained VT and 235 ± 27 ms in nonsustained VT. Mostly triple extrastimuli were needed to induce VT.

The mean doses of procainamide and lidocaine were 1050 mg and 161 mg, respectively. The mean plasma concentrations of procainamide and lidocaine were $7.5 \mu\text{g/ml}$ and $3.1 \mu\text{g/ml}$, respectively. All the patients who were given lidocaine showed disturbances of the central nervous system such as dysarthria and light headedness.

The induction of sustained VT was suppressed in 15 of 29 patients (52%) by procainamide, but in none by lidocaine (Table II). The induction of nonsustained VT was suppressed in 6 of 18 patients (33%) by procainamide, and in 1 of 8 patients (13%) by lidocaine (Table II). The efficacy of procainamide in suppression of VT induction was significantly higher than that of lidocaine ($p < 0.01$) (Table II). Fig. 1 shows the results of programmed electrical stimulation of a patient in whom both lidocaine and procainamide were tested respectively, and the former

Fig.1. Demonstration of a case in whom procainamide was shown to be effective while lidocaine to be ineffective in suppression of sustained VT induction by serial drug testing using programmed ventricular stimulation. Three surface electrocardiograms and one intracardiac electrogram from the right ventricular outflow tract (RV out) are recorded simultaneously. (A) In baseline, sustained polymorphic VT (SPVT) was induced by triple extrastimuli (S₁, S₂, S₃, S₄). (B) Post lidocaine sustained monomorphic VT (SMVT) remained inducible by triple extrastimuli. (C) Procainamide suppressed the induction of sustained VT and nonsustained VT of more than 10 beats.

proved to be ineffective, but the latter to be effective.

The electrophysiological effects of lidocaine and procainamide were compared (Fig. 2). The mean effective refractory periods of the right ventricle measured by the first extrastimulus (ERP-S₂), the second extrastimulus (ERP-S₃), and the third extrastimulus (ERP-S₄) were significantly prolonged by procainamide compared to the baseline state (ERP-S₂: 244 ± 23 ms vs 272 ± 26 ms, ERP-S₃: 196 ± 28 ms vs 230 ± 34 ms, ERP-S₄: 186 ± 25 ms vs 218 ± 30 ms, $p < 0.01$). The mean cycle length of induced VT was also prolonged significantly by procainamide compared to that before the drug application (240 ± 49 ms vs 304 ± 61 ms, $p < 0.01$).

In addition the mean HV interval, QRS interval during sinus rhythm and ventricular pacing at the same cycle length, and QTc interval were significantly prolonged by procainamide (HV interval: 46 ± 7 ms vs 56 ± 12 ms, QRS interval during sinus rhythm: 98 ± 20 ms vs 109 ± 23 ms, QRS interval during ventricular pacing: 172 ± 12 ms, vs 194 ± 17 ms, QTc interval: 412 ± 31 ms vs 478 ± 34 ms, $p < 0.01$). On the other hand lidocaine did not affect these electrophysiological parameters significantly.

In a certain number of cases, either one or both drugs showed worsening effects on the induction of arrhythmias. Fig. 3 shows a case in which the worsening effect of both lidocaine and procainamide were demonstrated. In this case

Fig.2. Comparisons in electrophysiological effects between procainamide and lidocaine. The mean effective refractory periods of the right ventricle measured by the first extrastimulus (ERP-S2 at RV), the second extrastimulus (ERP-S3 at RV), and the third extrastimulus (ERP-S4 at RV), the induced VT cycle length (CL), the HV interval, the QRS interval during sinus rhythm (SR) and ventricular pacing (VP), and the QTc interval were all significantly prolonged by procainamide (●), while they were not changed significantly by lidocaine (○).

nonsustained polymorphic VT was changed into sustained monomorphic VT to become inducible. The worsening effect was demonstrated in 8 of 18 cases (44%) with procainamide administration, and in 3 of 8 cases (38%) with lidocaine. There were no differences in the incidence of worsening effect between the two drug groups. Morphologic changes of induced VT from polymorphic into monomorphic form were seen in 5 of 6 cases (83%) of procainamide, and in 3 of 5 cases (60%) of lidocaine. In all of these cases, both drugs were proven to be ineffective or to aggravate arrhythmias.

Electrophysiological effects of procainamide were compared between the procainamide effective (21 cases, group I) and the ineffective

or worsening (26 cases, groups II) patients (Fig. 4). There were no significant differences between the two groups either in the baseline electrophysiologic parameters or those during the drug application. However, there was a tendency for the degrees of prolongation in the effective refractory periods of the right ventricle and QRS interval to be larger in group I than group II (Δ ERP-S2: 30 ± 16 ms vs 23 ± 17 ms, Δ ERP-S3: 38 ± 24 ms vs 30 ± 24 ms, Δ ERP-S4: 40 ± 18 ms vs 18 ± 21 ms, Δ QRS: 16 ± 19 ms vs 8 ± 8 ms, $P = \text{NS}$).

In 3 cases the combined effects of procainamide and lidocaine were studied. In 1 case, induction of sustained VT, which was inducible with 3 extrastimuli in the baseline, was abolished

Fig.3. Demonstration of a case in whom the worsening effects of procainamide and lidocaine were shown by serial drug testing. (A) In baseline, nonsustained polymorphic VT (NPVT) of 10 beats was inducible by triple extrastimuli. (B) (C) Post lidocaine and then procainamide, sustained monomorphic VT (SMVT) became to be inducible.

by procainamide, while sustained VT became inducible with only 2 extrastimuli after lidocaine was added. In the remaining 2 cases, the lidocaine application combined with procainamide did not enhance the suppressive effect of procainamide on VT induction, but it cancelled a prolonging effect of the effective refractory period of the right ventricle produced by procainamide to some degree.

DISCUSSION

Antiarrhythmic drug therapy still stands as the main therapeutic intervention for prevention of recurrent life-threatening ventricular tachyarrhythmias. At the present time, there are two major approaches to evaluating antiarrhythmic drug effects; the noninvasive and the invasive methods. A noninvasive approach, using repeated Holter monitoring and/or exercise testing

is based on the detection of spontaneous ventricular ectopic activity with complexity and high frequency. The rationale for employing this approach is that the abolition of triggering ventricular arrhythmias will prevent the occurrence of life-threatening ventricular tachyarrhythmias. The absence of frequent ventricular arrhythmias precludes the use of this noninvasive method. It is well known that a certain number of cases with recurrent sustained ventricular tachycardia do not have frequent ventricular arrhythmias detectable by Holter monitoring.^{24,25} In addition, the abolition of triggering arrhythmias as a goal of this method has not yet been established as a fully effective way to prevent recurrent sustained ventricular tachycardias.²⁶

The invasive approach is an electrophysiological test using programmed ventricular stimulation. The method has been used to identify the potential high-risk patients for sudden cardiac

Fig. 4. Comparison of electrophysiological effects of procainamide between the procainamide effective and ineffective or worsening groups. There was a tendency that the degrees of prolongation in the effective refractory periods of the right ventricle (ERP-S2, ERP-S3, ERP-S4) and QRS interval were larger in the procainamide effective group (●) than the ineffective or worsening group (■).

death including those who have had myocardial infarction. The method has also been used to select and prospectively evaluate antiarrhythmic regimens for treatment of recurrent sustained VT²¹⁻²⁴. In several studies including ours, the inducibility of sustained ventricular tachycardia has been shown to be useful in predicting the occurrence of spontaneous sustained ventricular tachycardia or sudden cardiac death^{9,10,18,27} although the predictive value and clinical significance of this technique remained to be determined. There is no way other than programmed electrical stimulation to disclose the substrate which allows the development of unidirectional block and delayed conduction essential to initiate and perpetuate reentrant tachyarrhythmias. The method is also useful in examining the effect of drugs on the reentry circuit. We investigated the effects of the most widely used antiarrhythmic agents, procainamide and lidocaine, on electrically inducible VT. The study was con-

ducted in patients at the post-acute phase of myocardial infarction in an effort to evaluate the usefulness and limitations of medical treatment in preventing life-threatening ventricular tachyarrhythmias.

In this study, the efficacy rate of procainamide was 45% in total VTs (52% in sustained VT and 33% in nonsustained VT), while that of lidocaine was 7% (0% and 13%, respectively). Procainamide was significantly more effective than lidocaine. These results are similar to those of other reports^{24,28-37} in which the efficacy rate of acute intravenous procainamide administration ranges from 13 to 48%^{24,28-37} and that of lidocaine from 5 to 19%^{24,28,31}. The variability in the results seems to be due to differences in patient selection, the stimulation protocol, the doses of the applied drugs and the evaluation criteria for drug efficacy. In our study, the patients were at the post-acute phase of myocardial infarction and most had no documented

episodes of recurrent sustained VT. The induced VT included both sustained and nonsustained type, and triple extrastimuli were used to examine inducibility of VT. In addition, VT was defined as 10 or more consecutive ventricular beats, and the drug was judged as effective even when sustained VT was changed into nonsustained VT inducible.

The mechanism of the majority of VT in the present study appears to be reentry, since they were repeatedly induced by the extrastimuli with certain limits of the coupling intervals. Some of them were also terminated by the extrastimuli (Table I). It is not completely ruled out, however, that abnormal impulse formation such as triggered-activity as a cause of the VT may play a role in the genesis of the induced arrhythmias in some of the cases. Procainamide is presumed to prevent reentrant tachyarrhythmias either by slowing conduction velocity in the area of depressed conduction and converting unidirectional block into bidirectional one, by prolonging refractory period in the reentry pathway or by a combination of both.^{29,33,34,36-38} In this study, while the effective refractory period of the right ventricle as well as the HV and QRS intervals reflecting intraventricular conduction time were significantly prolonged by procainamide, no correlation was found between the effects on VT inducibility and those on the effective refractory periods and the indicators of intraventricular conduction. These results agree with those reported by others.^{34,36,37} This may be explained by the fact that prolongation of the refractory period and conduction velocity were measured in the global ventricular tissue, and may not accurately reflect the effect within the reentry circuit of VT.^{34,36,37} At present it is not possible to evaluate the effects of antiarrhythmic agents on the reentry circuit itself. On the other hand lidocaine did not show any prolonging effects on either the refractory periods or the conduction velocity, which may explain different effects on the prevention of the VT inducibility between the two drugs.

In a considerable number of cases, nonsustained VT were converted into sustained VT inducible after the drug application. These proarrhythmic effects were demonstrated in 44% cases of the procainamide group and 38% of the lidocaine group. The incidence of proarrhythmic effects by procainamide has been reported to be in a range between 13 and

20%.^{29,34,35,38,39} The differences between our data and those of others are mostly attributed to the patient selection and the difference in the pacing protocol. The proarrhythmic effects of lidocaine have not been described in the literature and remain to be investigated. The potential mechanism of the proarrhythmic actions by the class I agents is indicated by their effects on the conduction velocity and the refractory period, both of which are related to their antiarrhythmic actions. Therefore, the proarrhythmic effects of these agents cannot be ignored whenever they are used.

In summary, the study demonstrated that procainamide representing class IA drugs was more effective than lidocaine representing class IB drug for the prevention of a potential life-threatening ventricular tachycardia in patients post myocardial infarction. However, its efficacy appeared to be considerably limited. Drug testing using programmed ventricular stimulation was shown to be a valuable method to confirm the effectiveness of antiarrhythmic agents and to exclude their proarrhythmic actions in each patients.

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