Original Article

Acute Effects on Signal-Averaged Electrogram Parameters and Suppressing Premature Ventricular Contractions in Single or Combined Use of Class I Antiarrhythmic Drugs

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Disopyramide (DP), mexiletine (MX), and flecainide (FL) are class I antiarrhythmic drugs. However, these drugs exert different effects on the electrocardiogram (ECG) based on their unique actions on cardiac myocytes. The electrocardiographic changes during combination therapy with these drugs are not well understood. The purpose of the present study was to evaluate acute morphologic changes in the ECG based on signal-averaged high resolution ECG (SAECG) after administration of the drugs in relation to their antiarrhythmic efficacy and safety. Twenty-one patients with frequent and stable premature ventricular contractions (PVC) were studied. Changes in the filtered QRS duration (f-QRS) and the root mean square voltage of the last 40 msec of the QRS complex (RMS40) were evaluated. Suppression of PVCs was achieved soon after intravenous administration of the drugs (63% for DP, 43% for MX, 86% for FL and 100% for DP+MX). Although DP and FL significantly prolonged f-QRS, MX had little effect on f-QRS. DP+MX also prolonged f-QRS, but the degree of prolongation was moderate. RMS40 was significantly decreased by DP and FL, but not by MX. DP+MX also decreased RMS40, but the decrease was less than for DP alone. Late potentials were observed after administration in 56% of patients with DP, 0% with MX, 67% with FL and 0% with DP+MX. No adverse events were reported during the study.

In summary, the class I antiarrhythmic drugs exerted different acute effects on SAECG parameters. The combination of DP and MX increased the efficacy on suppressing PVC without excess additive changes on SAECG parameters. We conclude that combination therapy with DP and MX is efficacious and safe in patients with PVC and the analysis of SAECG during antiarrhythmic therapy is clinically important.
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Key words: Class I antiarrhythmic drugs, Combination therapy, Signal-averaged electrocardiogram, Premature ventricular contractions

Introduction

Sodium channel blocking agents, known as class I antiarrhythmic drugs,[1] are being used worldwide as the first-line therapy for various clinical arrhythmias. These drugs have potential effects on the electro-

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cardiogram (ECG) as a reflection of their antiarrhythmic action or sometimes as an adverse proarrhythmic action. It is thought that these effects depend on their cellular electrophysiologic properties.

Class I antiarrhythmic drugs usually are divided into three subgroups; Ia, Ib and Ic,[2] and disopyramide (DP), mexiletine (MX), and flecainide (FL) are representative drugs of each respective subgroup. Based on their separate modes of action on cardiac myocytes, these drugs exert different effects on the electrocardiogram (ECG). Specifically, DP prolongs QRS duration and QT interval, MX has almost no effect, and FL mainly prolongs QRS duration.[3,4] However, the electrocardiographic changes during combination therapy with these drugs are not well understood.

The purpose of the present study was to evaluate acute morphologic changes of the ECG using signal-averaged high resolution ECG (SAECG) after administration of these drugs individually or in combination in relation to their antiarrhythmic efficacy and safety.

Patients and Methods

Patients

Twenty-one adult patients of medium build were enrolled in this study. All patients had >5/min stable premature ventricular contractions (PVC). Repeated Holter ambulatory monitoring recordings confirmed the appearance of PVC. All the PVCs were monomorphic and isolated during the study. None of the patients had organic heart disease or congestive heart failure. Informed consent was obtained from all patients before the study.

Administration of Antiarrhythmic Drugs

All antiarrhythmic drugs were given intravenously based on the following protocols:

- disopyramide (DP) 100 mg/5 min, n = 19
- mexiletine (MX) 125 mg/5 min, n = 21
- flecainide (FL) 75 mg/5 min, n = 7

Combination therapy was given in 7 patients who did not achieve sufficient suppression of PVC by DP alone or MX alone using the following protocol:

- DP+MX MX 125 mg/5 min immediately followed by DP 100 mg/5 min, n = 7

Each drug regimen was performed with a 1 or 2 week interval between regimens.

Evaluation of Antiarrhythmic Efficacy

We considered that a drug was "effective" when a >75% reduction of the number of PVC was obtained from 5 min to 20 min after the end of injection. The surface ECG was monitored continuously throughout the study.

Recording and Measurement of SAECG

SAECG was recorded immediately before and after each drug administration using an NEC-SANEI signal processor 7T18. On each occasion, more than 200 consecutive sinus beats were averaged to obtain a low-noise recording for the following measurements. The filtered QRS duration (f-QRS) and the root mean square voltage of the last 40 msec of the QRS complex (RMS40) were measured automatically for the averaged signals according to Simson's methods.[5] A late potential (LP) was defined as "positive" when the f-QRS was more than 120 msec based on the criterion of Gomes et al.[6]

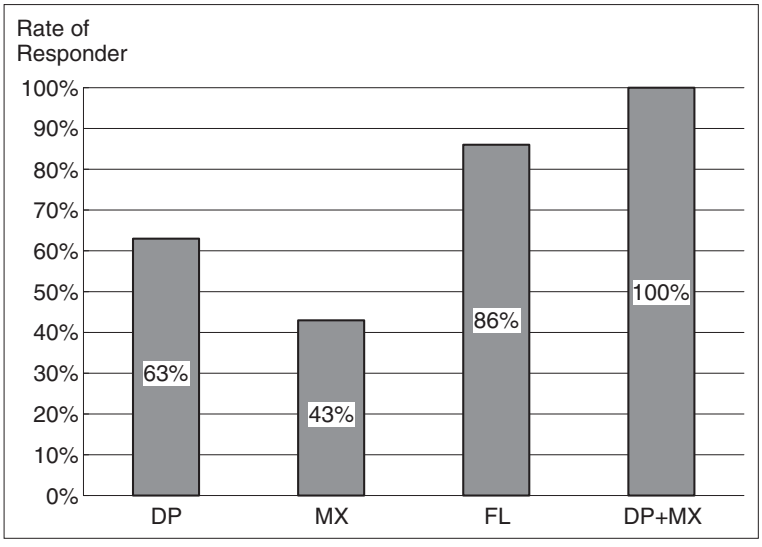

Figure 1 Antiarrhythmic efficacy against PVC.
DP: disopyramide, MX: mexiletine, FL: flecainide.

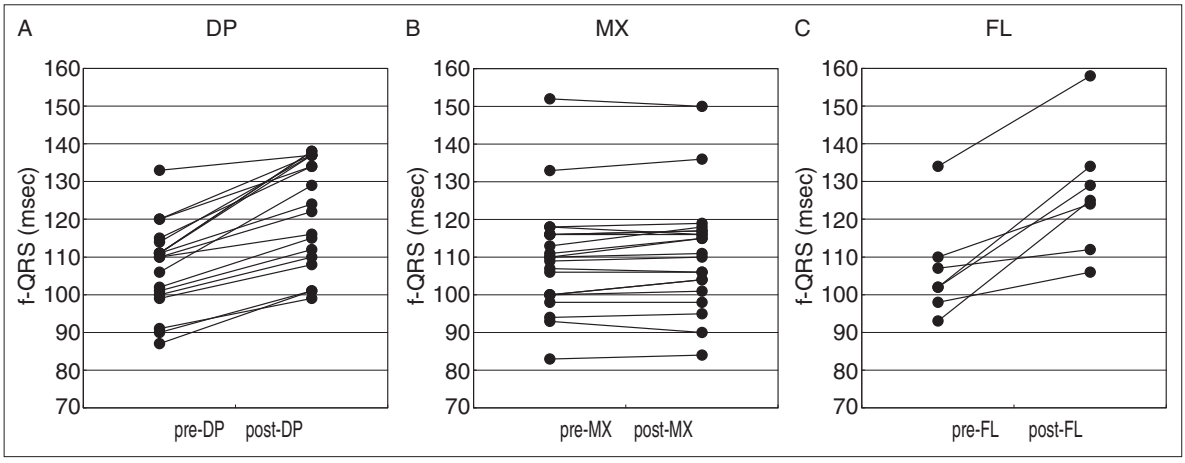

Figure 2 F-QRS before and after drug administration.
f-QRS: filtered QRS duration (msec). A. DP: disopyramide. B. MX: mexiletine. C. FL: flecainide.

Results

Antiarrhythmic Efficacy for PVC

Rates of response for each drug are shown in **Figure 1**. Acute suppression of PVC was achieved in 12 of 19 patients (63%) with DP, 9 of 21 (43%) with MX, and 6 of 7 (86%) with FL. Combination therapy with DP+MX, tested only in patients who did not respond to DP or MX alone, increased the antiarrhythmic efficacy, resulting in perfect suppression (7 of 7; 100%).

None of the patients had any worsening of PVC frequency or nature throughout the study.

Changes in f-QRS Immediately after Drug Administration

DP and FL both significantly prolonged f-QRS, but MX had almost no effect as shown in **Figure 2A, B, C** (DP: $107.5 \pm 11.4 \rightarrow 122.6 \pm 14.3$ msec; $p < 0.0001$, MX: $109.7 \pm 14.6 \rightarrow 110.9 \pm 14.6$ msec; $p < 0.05$, FL: $106.5 \pm 13.3 \rightarrow 126.9 \pm 16.8$ msec; $p < 0.005$). Combination therapy with DP+MX also significantly prolonged f-QRS. However, the magnitude of the change was less than that with DP alone as shown in **Figure 3** (DP: $16.4 \pm 4.7\%$, MX: $1.2 \pm 1.9\%$, DP+MX: $12.3 \pm 7.3\%$, DP vs. MX; $p < 0.0001$, MX vs. DP+MX; $p < 0.002$, DP vs. DP+MX; $p < 0.05$, respectively).

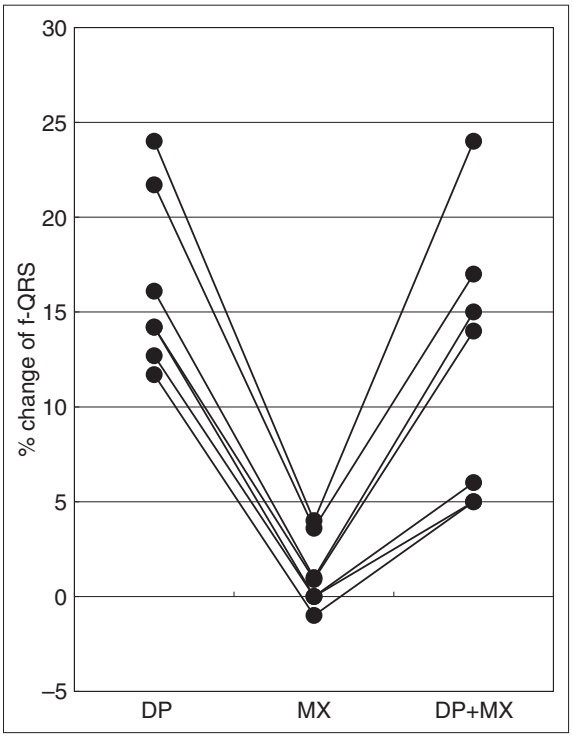

Figure 3 Comparison of percent change in the f-QRS between single drug and combination therapy.
f-QRS: filtered QRS duration, DP: disopyramide, MX: mexiletine, DP+MX: combination therapy with DP and MX.

Changes of RMS40 Immediately after Drug Administration

As shown in **Figure 4A, B, C**, DP and FL markedly decreased RMS40 in all patients (DP: $13.0 \pm 11.1 \rightarrow 7.7 \pm 7.9$ microvolt; $p < 0.0001$, FL: $14.9 \pm 12.5 \rightarrow 6.3 \pm 6.5$ microvolt; $p < 0.02$, for all). MX did not exert uniform effects on RMS40, resulting in almost no change in the mean value (MX: $11.1 \pm 11.2 \rightarrow 9.9 \pm 11.4$ microvolt; n.s.). Though DP+MX also significantly decreased RMS40, the change was less than that with DP alone (DP: $-49.4 \pm 15.9\%$, MX: $-13.0 \pm 15.7\%$, DP+MX: $-29.6 \pm 26.9\%$, DP vs. MX; $p < 0.0001$, MX vs. DP+MX; n.s., DP vs. DP+MX; $p < 0.01$; **Figure 5**).

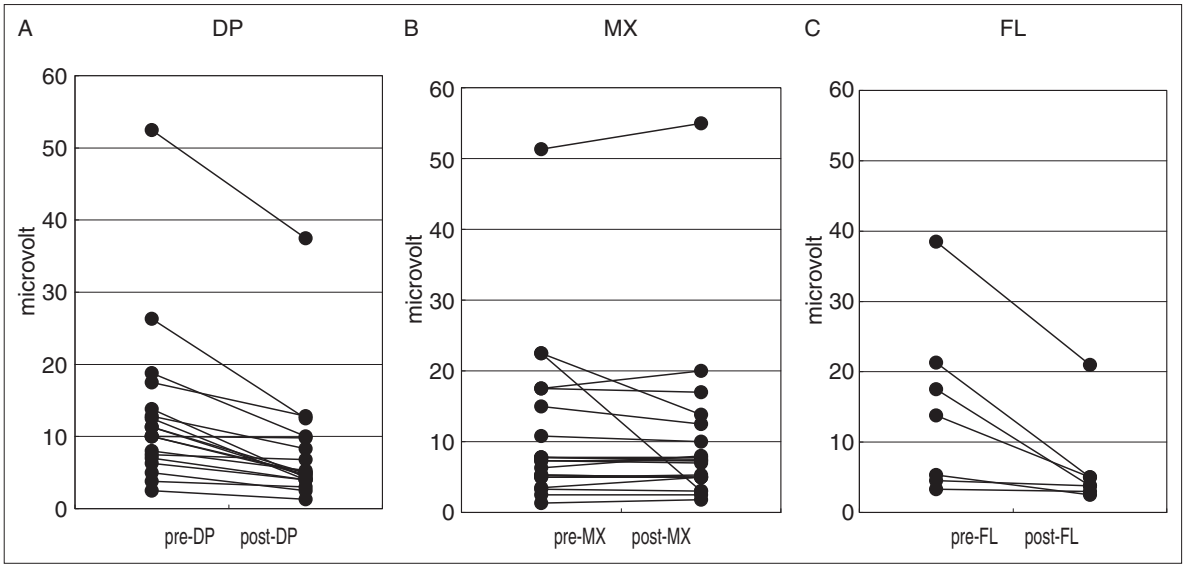

Figure 4 RMS40 before and after drug administration.
RMS40: root mean square voltage during last 40 msec (microvolt). A. DP: disopyramide. B. MX: mexiletine. C. FL: flecainide.

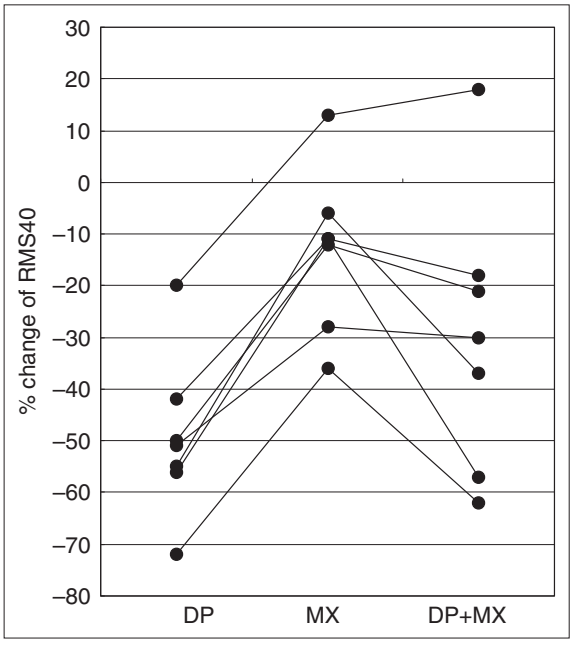

Figure 5 Comparison of percent changes in the RMS40 between single drug and combination therapy.
RMS40: root mean square voltage during last 40 msec (microvolt), DP: disopyramide, MX: mexiletine, DP+MX: combination therapy with DP and MX.

LP Evaluation

The LP was positive in 2 of 21 patients. But it became positive after administration of drugs in 10 (56%) of 18 patients receiving DP, 0 (0%) of 19 patients receiving MX, 4 (67%) of 6 patients receiving FL, and 0 (0%) of 6 patients receiving DP+MX. Thus, combined use of DP and MX diminished the effect on conduction delay without weakening antiarrhythmic efficacy on suppressing PVCs.

Discussion

Influence of Individual Antiarrhythmic Drugs on SAECG Parameters

Changes in f-QRS and RMS40 after the administration of class I antiarrhythmic drugs reflect the differential mechanism of actions on the Na channel for each drug.[3] Since DP has a slow kinetic nature and FL has a very slow kinetic nature in combining with and dissociating from Na channels, they exert strong Na channel blocking action not only at high heart rates but also at low heart rates.[7] Blockade of Na channels reduces the rate of rise and amplitude of the action potential, resulting in a depression in the conduction velocity from cell to cell. This must influence the duration of the QRS complex, although the changes may be trivial. As a result, significant prolongation of the f-QRS and a decrease in the RMS40 occur even in sinus rhythm.

In contrast, MX has almost no effect on these parameters. This can be explained by the fact that MX is a fast kinetic drug. Since MX is thought to dissociate very rapidly from Na channels, it may not have enough time to effect the ECG during sinus beats, which have relatively slow rates.

In the clinical setting, we occasionally find that the QRS width on the surface ECG is often widened

during long-term treatment by class Ia or Ic drugs, including DP or FL, but not widened by class Ib drugs, like MX or lidocaine. The present study may support this clinical observation from another point of view based on SAECG, although we were evaluating acute effects of the drugs.

Effects of Combination Therapy with DP+MX on SAECG Parameters

DP blocks Na channels in the activated state with a slow kinetic nature. In contrast, MX exerts its Na channel blocking action in the inactivated state with a fast kinetic nature.[8] Since their Na channel blocking actions are complementary, they may have additive or synergistic effects when DP and MX are used concomitantly.[9]

Previous reports have described combination therapy with class Ia and class Ib agents[10,11] and most of these reports indicate the superiority of these combination therapies.[12–14] DP+MX is one of the most frequently used combination. The present study also clearly showed the synergistic effect of DP+MX in treating PVC.

It is believed that a main part of the antiarrhythmic action may come from the suppression of Na channels in ventricular myocytes. A stronger and/or wider spectrum of Na channel suppression can increase the antiarrhythmic efficacy in the clinical setting, in which the state of the Na channels may be inhomogeneous and unstable in the diseased heart.

As stated above, class Ia or Ic drugs definitely change SAECG parameters. Since LP, which is one of the most powerful predictors of severe ventricular arrhythmias, is defined as "positive" with a wide f-QRS and low RMS40,[5,15–17] an excess prolongation of f-QRS and/or an extreme decrease in the RMS40 may be related to the arrhythmogenicity.

From a clinical point of view, excess changes in SAECG parameters (a prolongation of f-QRS with a decrease of RMS40) make the LP positive and may lead to the appearance of arrhythmias because the impulse conduction becomes slower or more inhomogeneous.[18] Fortunately, we never found any worsening of arrhythmias or new severe arrhythmias in our study, but the change in the LP from negative to positive occurred in 56% of patients receiving DP and in 67% of patients receiving FL. However, it occurred in 0% of patients during combination therapy with DP+MX in our series. Although DP+MX also prolonged the f-QRS and decreased RMS40, the magnitude of those changes with DP+MX was much smaller than those with DP alone. The change after DP+MX was never additive or even significantly reductive. In other words, DP+MX exerted a protective effect against proarrhythmias, which should be avoided. This fact supports the safety of the combination therapy.[19,20]

Study Limitations

This study was designed to evaluate short-term changes in SAECG parameters immediately after administration of antiarrhythmic drugs. We do not know whether similar changes may occur during long-term use of these drugs in the clinical setting. Since we used fixed doses of each drug to simplify the study protocol, no correction of the doses per body weight was performed. Body weights of all the patients were within a normal range. Although we did not check the serum concentration of these drugs, we believe that the concentrations were within the clinically-effective range during the study in each case. The changes of SAECG parameters at several lower doses of drugs should be checked to know a cut-off-point from receiver operating characteristic curve.

Another limitation of the present study is that patients were not randomized. The number of the patients in this study is small because patients who have stable and reproducible PVC for hours to days are quite rare in a single institution. Further objective evaluation with large-scale multicenter trials will be needed.

Acknowledgments

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