Antiarrhythmic Drug Combinations in the Treatment of Ventricular Tachycardia
Efficacy and Electrophysiologic Effects

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SUMMARY Combinations of antiarrhythmic drugs are frequently used to treat refractory ventricular tachycardia (VT), but few scientific data support this practice. We examined the efficacy and electrophysiology of 110 antiarrhythmic drug combination trials at electrophysiologic study in 74 patients with recurrent ventricular tachycardia. Lidocaine was combined with quinidine in 33 trials, procainamide in 22 and encainide in 20. Propranolol was combined with quinidine in 17 trials, procainamide in 12 and encainide in 6. All individual drugs tested (except propranolol, which was usually not tested individually) had failed at electrophysiologic study or clinically in the presence of usually accepted plasma concentrations. Lidocaine in combination with quinidine was effective in 3% of the trials, with procainamide in 5% and with encainide in none of the trials. Propranolol in combination with quinidine was effective in 18% of the trials, with procainamide in 17% and with encainide in none of the trials. The electrophysiologic effects of the tested drug combinations were dominated by the individual effects of the type 1 antiarrhythmic agents. We conclude that the tested antiarrhythmic drug combinations are infrequently effective in preventing VT induction at electrophysiologic study when each agent has failed individually. The addition of lidocaine or propranolol to quinidine, procainamide or encainide does not produce significant synergistic or new effects on the electrophysiologic variables analyzed.

COMBINATIONS of antiarrhythmic drugs are frequently used for acute and chronic treatment of refractory ventricular arrhythmias. These combinations usually consist of drugs that are ineffective when used individually. Use of combinations of individually ineffective drugs is based on the hypothesis that there may be additive, synergistic or new effects that exceed those of each drug used alone. The use of combinations of antiarrhythmic drugs for refractory arrhythmias has been recommended in several reports.1-4 Clinical efficacy in small groups of patients has been demonstrated.5-10 Most authorities do not recommend drug combinations as first-line treatment, and usually insist that conventional antiarrhythmic agents in adequate doses must have failed first. Addition of a second drug may antagonize a useful electrophysiologic action of the first drug, and may at the same time have fully additive toxic effects.3 The efficacy of antiarrhythmic drug combinations is poorly documented, especially in the treatment of ventricular arrhythmias.2 Ventricular tachycardia (VT) induction at electrophysiologic study in patients with symptomatic recurrent episodes of VT provides a means of rapid, objective evaluation of acute drug efficacy.8-12 In this study, we systematically analyzed the efficacy and electrophysiology of several drug combinations commonly used in the treatment of VT, using prevention of VT induction at electrophysiologic study as an indicator of drug efficacy.

Methods

Patients

We retrospectively analyzed all patients with recurrent VT studied in our electrophysiology laboratory. Patients were included in this study if they satisfied the following criteria: (1) Clinically recurrent VT. (2) The diagnosis of VT was confirmed at electrophysiologic study. (3) VT could be induced reproducibly in the absence of antiarrhythmic drugs. (4) Lidocaine was tested in combination with either quinidine, procainamide, or encainide, and each drug (including lidocaine) had failed individually at electrophysiologic study. Lidocaine was not tested individually at electrophysiologic study in 18 of 48 patients. All 18 patients had failed lidocaine clinically in the presence of usually accepted plasma levels. (5) Propranolol was tested in combination with either quinidine, procainamide, or encainide when each of these type 1 agents had failed at electrophysiologic study.

Because of the sequence of drug testing in our laboratory, propranolol was usually tested at the same electrophysiologic study at which another drug had failed, and thus was rarely tested alone.12 Thus, propranolol was generally tested in combination with other drugs and efficacy of propranolol alone was not usually determined.

Seventy-four patients, 69 males and five females, satisfied these criteria. Their mean age was 58 ± 13 years. Sixty-three patients suffered from sustained VT and 11 had nonsustained VT (six beats or more of VT lasting less than 15 seconds). Fifty-five patients had
coronary artery disease, seven cardiomyopathy, two valvular heart disease and five other forms of heart disease. Five patients showed no evidence of myocardial or valvular disease.

Electrophysiologic Study

Our methods for electrophysiologic study and determination of antiarrhythmic drug efficacy have been reported. In brief, antiarrhythmic drugs that prevented induction of VT despite use of the full stimulation protocol were considered effective. The stimulation protocol consisted of up to three ventricular extrastimuli delivered in spontaneous supraventricular or paced ventricular rhythm, use of several basic ventricular cycle lengths, and burst ventricular pacing to cycle lengths of \( \leq 280 \text{ msec} \). The most effective site for VT induction was determined at the initial electrophysiologic study and was used in subsequent reinduction studies. Efficacy was defined as induction of five or fewer beats of VT after antiarrhythmic drug administration. In patients with unsustained VT in the absence of antiarrhythmic drugs, efficacy was defined as induction of no more than two repetitive beats of ventricular origin after administration of antiarrhythmic drugs.

Antiarrhythmic Drug Combination Trials

Lidocaine was tested in combination with quinidine in 33 cases, procainamide in 22 and encainide in 20. Propranolol was tested in combination with quinidine in 17 cases, procainamide in 12, and encainide in six. Fifty of the 74 patients underwent one drug combination trial, 14 underwent two, eight underwent three and two underwent four trials.

Antiarrhythmic Drug Administration

Intraarterial pressure was monitored continuously during i.v. drug administration.

Lidocaine was given as a 100–150 mg bolus, followed by institution of a 4-mg/min i.v. infusion, then a further 25–50 mg bolus. Mean loading doses of lidocaine for combinations with quinidine, procainamide and encainide were 129 ± 36 mg, 137 ± 58 mg, and 146 ± 40 mg, respectively. These means (and those for propranolol) were not significantly different on an absolute or per-kilogram basis.

Propranolol was given intravenously at a rate of 1 mg/min. Mean total propranolol doses for combinations with quinidine, procainamide and encainide were 10.3 ± 3.0 mg, 9.7 ± 2.1 mg, and 11.8 ± 4.6 mg, respectively. Oral propranolol was used for combination testing in only four cases. Doses ranged from 80 to 480 mg/day, and were the maximum tolerated clinically.

Modes of administration and mean doses of quinidine, procainamide and encainide are shown in table 1. Intravenous quinidine was infused over 20 minutes and procainamide over 30 minutes. Intravenous encainide was administered over 15 minutes. Saline fluid replacement was commenced if hypotension occurred (systolic pressure < 90 mm Hg). Hypotension necessitated longer infusion periods in some patients.

Blood samples were drawn for determination of plasma concentrations of antiarrhythmic drugs at the conclusion of electrophysiologic testing of each drug and each drug combination. Plasma levels of propranolol and encainide were not measured.

Variables Analyzed

The following variables were measured and analyzed according to standard definitions: sinus cycle length, PR interval, QRS duration, corrected QT interval (Bazett's formula), AH and HV intervals, mean arterial pressure, right ventricular effective refractory period (VERP), and the basic cycle length at which VERP was determined. The complexity of stimulation required for VT induction was assessed using the following arbitrary index to facilitate statistical analysis. Spontaneous VT was given a score of 0. VT induction with slow (cycle length \( \geq 400 \text{ msec} \)) fixed rate ventricular pacing was given a score of 1. Inductions with one, two or three extrastimuli were given scores of 1, 2 or 3, respectively, and an extra point was added if the extrastimuli were delivered during ventricular drive. A score of 5 was given for VT induction with rapid-burst ventricular pacing. This hierarchical index corresponds to the order in which these stimulation programs are applied in our laboratory. Four variables related to VT were also analyzed: mean arterial pressure during VT, number of morphologies observed on the recorded surface and intracardiac leads, duration,

| Table 1. Dose and Plasma Levels of Type I Agents Tested in Combination with Lidocaine or Propranolol |
|----------------------------------------------------------|---------------------------------|-----------------|-----------------|
| Dose (mg)                                                | I.V. (no. of cases)             | Oral (no. of cases) | Plasma level (μg/ml) |
| Combinations with lidocaine                             |                                 |                  |                  |
| Quinidine                                               | 661 ± 172 (28)                  | 1900 ± 539 (5)   | 2.5 ± 1.1        |
| Procainamide                                            | 996 ± 217 (12)                  | 4278 ± 2492 (10) | 7.1 ± 2.7        |
| Encainide                                               | 84 ± 21 (9)                     | 198 ± 39 (11)    | *                |
| Combinations with propranolol                           |                                 |                  |                  |
| Quinidine                                               | 572 ± 163 (13)                  | 1600 ± 283 (4)   | 3.4 ± 2.5        |
| Procainamide                                            | 1017 ± 191 (6)                  | 3438 ± 515 (6)   | 9.7 ± 2.1        |
| Encainide                                               | 88 ± 25 (4)                     | 200 ± 0 (2)      | *                |

*Encainide plasma levels were not measured.
and mode of termination (spontaneous, by pacing or by DC cardioversion).

Since this is a retrospective study, all variables were not available for each drug test in every patient. A single ventricular catheter and intraarterial pressure monitoring were used for follow-up electrophysiologic studies to evaluate drug efficacy. His bundle electrograms were not routinely recorded at these studies. VERP was often not compared at identical basic cycle lengths; thus, the cycle length at which VERP was determined was also analyzed in all comparisons.

Using the above variables, we made the following comparisons: (1) Effects of lidocaine alone vs control (no drugs) (48 patients). (2) Effects of quinidine alone vs control (42 patients). (3) Effects of procainamide alone vs control (23 patients). (4) Effects of encainide alone vs control (22 patients). (5) Effects of quinidine, procainamide, or encainide in combination with lidocaine vs the effects of the former agent alone. This analysis was done separately for each of the three drugs. (6) Effects of quinidine, procainamide or encainide in combination with propranolol vs the effects of the former agent alone (again, analyzed separately for each of the three drugs).

Only paired data were used in comparisons.

The paired t test was used for testing continuous variables and chi-square contingency tables were used for discrete variables. A p value < 0.05 was considered statistically significant. Values are mean ± so.

Results

Plasma Levels of Antiarrhythmic Drugs

The mean plasma level of lidocaine at the conclusion of electrophysiologic testing of lidocaine in combination with quinidine was 3.5 ± 1.7 μg/ml, with procainamide 3.4 ± 1.3 μg/ml and with encainide 3.7 ± 0.8 μg/ml. Plasma levels of quinidine and procainamide at the conclusion of electrophysiologic testing of combinations of these drugs with lidocaine or propranolol are shown in table 1.

Efficacy

Table 2 is a summary of acute efficacy at electrophysiologic study of the tested drug combinations. The combination of lidocaine with quinidine, procainamide or encainide was effective in only two patients. Oral tocainide was substituted for lidocaine in these combinations, but proved ineffective at a subsequent clinical trial in one case and at repeat electrophysiologic study in the other. Only one of the five patients with effective propranolol combinations had failed propranolol alone. Long-term therapy with an acutely effective propranolol combination was attempted in one case (propranolol plus quinidine), but failed due to recurrent sustained VT.

Effects on Electrophysiology and Arterial Pressure

Individual Drugs

The individual actions of tested drugs are summarized in figure 1. Compared with control (off-drug) measurements, lidocaine produced a decrease in sinus cycle length, minor increases in QRS duration and corrected QT, a small decrease in AH interval, a small rise in mean arterial pressure, prolongation of VT cycle length, and an increase in VT induction index (all p < 0.05). Quinidine produced a decrease in sinus cycle length, an increase in QRS duration, a decrease in AH interval, prolongation of the HV interval, a small increase in mean arterial pressure, and an increase in VERP (all p < 0.05). Procainamide produced effects similar to but less marked than those of quinidine. Encainide produced a prolongation of PR interval, QRS duration, corrected QT interval, AH interval and HV interval, a small increase in mean arterial pressure, and prolongation of VT cycle length (p < 0.05).

One would anticipate fewer morphologies of VT and a lower incidence of cardioversion after drug administration, since only one episode of VT induction was necessary to confirm drug failure, while in pre-drug testing induction of at least three episodes of VT was required. Although only one episode of VT was induced after drug administration, multiple morphologies were frequently induced by attempts at pace termination. These morphologies were included in analysis. The incidence of multiple morphologies of VT was significantly lower only after lidocaine: 15% vs 40% before drug (p < 0.01). Similarly, need for cardioversion to terminate VT was reduced only after quinidine: 9% vs 36% before drug. No statistically significant changes occurred in the number of morphologies of VT or need for cardioversion after administration of the other antiarrhythmic drugs.

Combinations

The combination of lidocaine with quinidine, procainamide or encainide produced very few changes compared with the effects of the latter drugs alone. Addition of lidocaine to quinidine produced a 4-mm Hg increase in mean arterial pressure (p < 0.05), but no other significant changes. Addition of lidocaine to procainamide produced a 20-msec increase in VT cycle length (p < 0.05) and a 6-mm Hg rise in mean arterial pressure (p < 0.05), but no other significant changes. Addition of lidocaine to encainide increased QRS duration by 17 msec (p < 0.005), VERP by 11 msec (p < 0.05) and VT cycle length by 47 msec (p < 0.005). The remaining variables did not change. Propranolol combined with quinidine, procainamide or encainide caused additional changes in only two variables compared with the individual actions of the

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latter drugs. Sinus cycle length increased by 186 msec with quinidine ($p < 0.001$), 209 msec with procainamide ($p < 0.001$) and 116 msec ($p < 0.005$) with encainide. PR interval increased by 16 msec with quinidine ($p < 0.05$), 14 msec with procainamide ($p < 0.05$) and 28 msec ($p < 0.02$) with encainide. None of the remaining variables changed significantly.

**Adverse Reactions**

No serious adverse reactions occurred with the drug combinations tested. Propranolol was well tolerated even though many patients had severely compromised left ventricular function. (Only frank clinical left ventricular failure was considered a contraindication.) This low incidence of serious side effects relates to slow, careful drug administration with continuous intravascular pressure monitoring. Drug infusions were ceased if hypotension failed to respond to fluid replacement and slowed infusion.

**Discussion**

We found remarkably low efficacy rates for lidocaine in combination with quinidine, procainamide or encainide, using prevention of VT induction at electrophysiologic study as the indicator of drug efficacy. The efficacy rates for propranolol combinations were somewhat higher, but most of these patients had not been proven to be unresponsive to propranolol alone. Acute efficacy rates for single drug trials in our laboratory are 13% for lidocaine, 20% for quinidine, 19% for procainamide, 9% for encaïnide, 27% for propranolol, 11% for amiodarone, 10% for lorcainide and 12% for other agents. The acute efficacy rates for propranolol combinations in the current study are therefore similar to those of single drugs, and may represent actual individual efficacy of propranolol. In any event, use of propranolol in combination in this group of patients was not superior to the general acute efficacy of propranolol alone. Dreifus et al. reported that quinidine in combination with propranolol was clinically effective in treating two patients with VT. Each drug had failed individually. Fors et al. reported successful use of quinidine and propranolol in eight of 11 clinical trials of this combination in patients with VT. Nine of them had failed propranolol alone, and all were considered to have failed quinidine alone. Winkle et al. found drug combinations successful in only one of nine clinical trials in patients with VT. Fisher found drug combinations of various types to be "protective" at electrophysiologic study in 22 of 42 patients (if digoxin is ignored as a ventricular antiaarrhythmic agent). A significant proportion of these patients were not completely protected (using a similar definition to that we used for efficacy) and a large number of drug combinations were tested before a partially or completely protective combination was found. Duffy et al. tested two type 1A drugs in combination (chosen from quinidine, procainamide and disopyramide) in eight patients with recurrent VT. In no case did the combination prevent VT induction at electrophysiologic study.

Overall, considering only studies in which the total number of trials was reported and individual drug failure was established on rigorous grounds (using plasma drug levels where possible), drug combinations have been reported to be successful infrequently when each individual drug had failed. Lown and Graboys advo-

**Figure 1.** Changes in electrophysiologic variables and arterial pressure produced by lidocaine, quinidine, procainamide, and encainide when used individually. All changes are relative to control measurements made in the absence of antiarrhythmic drugs. SCL = sinus cycle length; PR = PR interval; QRS = QRS duration; QTc = corrected QT interval; AH = AH interval; HV = HV interval; MAP = mean arterial pressure; VERP = ventricular effective refractory period; BCL\textsubscript{VERP} = driving cycle length at which VERP was determined; VT \textit{CL} = ventricular tachycardia cycle length; VT \textit{MAP} = mean arterial pressure during VT.
cated using combinations of individually effective antiarrhythmic drugs to provide a "failsafe" mechanism; we did not test this concept in our study.

The combination of quinidine with propranolol has been evaluated in two canine studies of atrial and ventricular arrhythmias. In both studies, the combination had additive effects compared with the individual drugs in protecting against atrial arrhythmias, but not against ventricular arrhythmias. Our results with clinical VT therefore agree with these canine studies.

The limitations of the method of drug efficacy that we used in this study should be considered. Acute drug efficacy at electrophysiologic study correlates well with long-term antiarrhythmic drug efficacy in patients with VT. However, electrophysiologic study may not predict long-term drug inefficacy as accurately. Mason and Winkle reported a 33% efficacy rate after 6 months and an 11% efficacy rate after 18 months of follow-up in patients treated with drugs predicted to be ineffective at electrophysiologic study. Amiodarone is frequently effective in the long term, although it does not suppress VT induction with acute drug testing. Thus, potentially effective drugs may be discarded on the basis of electrophysiologic study in some patients. Nevertheless, electrophysiologic study provides a systematic, objective means of assessing drug efficacy over a short time in controlled circumstances in patients with potentially lethal arrhythmias. Plasma levels during acute drug testing in this study were in the usually accepted range; use of higher doses may have led to an increased incidence of drug success. Greenspan and colleagues demonstrated an increased success rate with higher-than-normal doses of procainamide. Furthermore, chronic oral antiarrhythmic therapy may be more effective than acute i.v. testing because of accumulation of electrophysiologically active metabolites, or suppression of ectopic beats that trigger the sustained arrhythmia. These limitations must be considered when translating our data to clinical management.

Electrophysiologic Effects

VT induction studies do not provide ideal circumstances for retrospective analysis of electrophysiologic effects of antiarrhythmic drugs. Induction of VT, hypotension during VT and possible cardioversion could alter autonomic tone and thereby affect variables subject to autonomic influence. Nevertheless, the electrophysiologic changes after individual drugs in this study were similar to those reported by other investigators, suggesting that the data are valid. Unusual changes in the case of lidocaine were minor prolongation of QRS duration and corrected QT interval and shortening of AH. The latter was most likely not a direct effect of lidocaine. High doses of lidocaine and lidocaine in the presence of physiologic potassium concentrations depress conduction velocity, and high plasma levels would have been present when these variables were measured in our study just minutes after bolus injection. Furthermore, lidocaine may depress conduction in diseased tissues, and most of our patients had extensive myocardial disease. Thus, minor prolongation of QRS duration is consistent with animal and cellular electrophysiologic studies. Lidocaine usually shortens action potential duration; the reasons for minor QTc prolongation in this study are not clear.

Encainide produced two unusual effects compared with previous i.v. studies. The QTc was prolonged in excess of an increase in QRS duration, and the AH interval was lengthened. These changes have been described in patients receiving oral encainide and are probably metabolite effects. Twelve of our 22 patients were tested on oral encainide.

The electrophysiologic effects of the tested drug combinations were dominated by the individual effects of quinidine, procainamide or encainide, with minor additional effects due to the added drug. For lidocaine combinations, VT cycle length was the most consistently affected electrophysiologic variable. The greatest number of additional effects of lidocaine occurred in combination with encainide (prolonged QRS duration, VERP and VT cycle length). Addition of propranolol to quinidine, procainamide or encainide slowed sinus cycle length and prolonged PR interval, but produced no other significant changes. These findings argue against the presence of major additive (or antagonist) electrophysiologic effects in ventricular tissues due to the drug combinations. Dreifus et al. studied the effects of drug combinations in the isolated rabbit heart and found that the addition of lidocaine to procainamide reduced the rate of phase 0 depolarization. Addition of propranolol to quinidine also caused further decrease in the rate of phase 0 depolarization and prolongation of action potential duration. Hondegem and Katzung found the combination of lidocaine with quinidine to cause further depression of phase 0 depolarization of premature extrasystoles in guinea pig papillary muscles, but noted no other additive effects.

Our study suggests that any additive effects of drug combinations at therapeutic plasma concentrations do not cause major electrophysiologic changes in ventricular tissues in man, at least in terms of the variables examined in this study. The combination of lidocaine with encainide may be a possible exception, and further study of this interaction is required.

Clinical Implications

The six antiarrhythmic drug combinations tested in this study were rarely effective in preventing VT induction at electrophysiologic study when each drug had failed individually. If other studies confirm that drug combinations are rarely successful when each drug has failed individually, a reappraisal of serial testing of drug combinations would be in order. A mathematically large number of drug combinations could be tested, side effects are often additive without necessarily increasing antiarrhythmic potency, and the yield in return for patient discomfort and physician time may be poor. A more rational approach is systematic testing of individual drugs in maximal tolerated
doses, followed by consideration of alternative forms of treatment, such as mapping-directed arrhythmia surgery, antitachycardia pacemakers, or implantable defibrillators. Exhaustive testing of drug combinations might best be reserved for patients who are poor candidates for nonpharmacologic treatment.

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