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Insights Into the Electrophysiology Study Versus Electrocardiographic Monitoring Trial: Its Programmed Stimulation Protocol May Introduce Bias When Assessing Long-Term Antiarrhythmic Drug Therapy

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Objectives. **We hypothesized that if the Electrophysiology Study Versus Electrocardiographic Monitoring (ESVEM) trial programmed stimulation protocol misclassified some drug trials as effective, then the misclassification rate would be proportionally greater for drugs other than sotalol.**

Background. **In the ESVEM trial, patients treated with sotalol had fewer arrhythmic recurrences than those treated with other antiarrhythmic drugs despite similar efficacy predictions during electrophysiologic testing.**

Methods. **We retrospectively compared the standard programmed stimulation protocol used at Case Western Reserve University, which used three extrastimuli during all follow-up studies, with the ESVEM protocol in 176 antiarrhythmic drug trials: sotalol (n = 54), procainamide (n = 73) and quinidine/mexiletine (n = 49).**

Results. **Predictions of efficacy were higher in the sotalol trials (14 of 54 standard, 20 of 54 ESVEM) than in procainamide trials (7 of 73 standard, 14 of 73 ESVEM) or quinidine/mexiletine trials (1 of 49 standard, 7 of 49 ESVEM). Thus, the two protocols classified 19 of 176 trials differently: not effective by the standard protocol but effective by the ESVEM trial. Discordant predictions of drug efficacy constituted a smaller proportion of ESVEM protocol efficacy predictions for sotalol (6 [30%] of 20) than for the other drugs (13 [62%] of 21, $p \leq 0.05$).**

Conclusions. **In the present study, the ESVEM programmed stimulation protocol predicted efficacy more often than the standard protocol. Discordant predictions represented a smaller portion of efficacy predictions for sotalol than for the other drugs. Thus, in the ESVEM trial, the superior long-term follow-up observed in patients assigned to sotalol may have been an artifact of the stimulation protocol utilized by the ESVEM investigators.**

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In the Electrophysiology Study Versus Electrocardiographic Monitoring (ESVEM) trial (1), serial electrophysiologic testing was compared with serial 24-h ambulatory (Holter) monitoring for guiding antiarrhythmic drug treatment of ventricular tachycardia. Sotalol suppressed induction of ventricular tachycardia more often than the other drugs utilized in the study (35% vs. 16%). The efficacy of sotalol in suppressing the induction of ventricular tachycardia in other studies has been consistent at ~35% (2,3). However, these studies utilized different stimulation protocols and included patients with diverse clinical characteristics.

A somewhat surprising finding in the ESVEM trial was that among patients whose therapy was guided by electrophysiologic study, sotalol was associated with fewer arrhythmia recurrences than other antiarrhythmic drugs (30% vs. 60%, respectively, at 2 years) despite equivalent electrophysiologically guided efficacy predictions. The reason for this difference was not clear. According to the ESVEM investigators, this finding suggested that sotalol had unique effects that were not identified by electrophysiologic studies.

The ESVEM programmed stimulation protocol utilized only two rather than three ventricular extrastimuli during follow-up studies when either one or two ventricular extrastimuli induced ventricular tachycardia during the baseline study. The ESVEM programmed stimulation protocol utilized three ventricular extrastimuli during follow-up studies only when three extrastimuli induced ventricular tachycardia at the baseline study. Previous studies (4,5) have shown that the number of extrastimuli necessary to induce ventricular tachycardia may vary. We hypothesized that the ESVEM programmed stimulation protocol classified drugs as effective during some trials that utilized only up to two extrastimuli when ventricular tachycardia would have been induced with three extrastimuli. Furthermore, we hypothesized that the nature of the ESVEM programmed stimulation protocol was responsible for the lower arrhythmia recurrence rate in patients taking sotalol compared with those taking other antiarrhythmic drugs. To test these hypotheses, we compared the ESVEM criteria for predicting antiarrhythmic drug efficacy for

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ventricular tachycardia to criteria reported by other investigators and used at our institution (standard protocol) (6,7). The standard protocol uses up to three extrastimuli at two right ventricular sites in all drug trials regardless of the results of the baseline study.

Methods

We analyzed the results of electrophysiologic studies in 125 patients who presented to University Hospitals of Cleveland/Case Western Reserve University with sustained ventricular tachycardia, after an aborted cardiac arrest or with syncope between 1989 and 1992. Each of the patients met the eligibility enrollment criteria for the ESVEM trial (8). Each patient underwent programmed ventricular stimulation in the absence of antiarrhythmic drugs (baseline study) using a protocol that included up to three premature extrastimuli from two right ventricular sites after an 8-beat paced drive train at two cycle lengths. Double extrastimuli were completed at both sites before three extrastimuli were used. Sustained monomorphic ventricular tachycardia was induced and reinduced during the baseline study in each patient.

Each patient underwent one or two serial follow-up electrophysiologic studies in an attempt to find a drug that suppressed induction of ventricular tachycardia. Each follow-up study included up to three extrastimuli at two ventricular sites and two paced drive train cycle lengths regardless of the number of extrastimuli required to induce ventricular tachycardia during the baseline electrophysiologic study. Double extrastimuli were completed at both sites before three extrastimuli were used. Antiarrhythmic drug efficacy using this protocol (standard protocol) was defined as inability to induce sustained ventricular tachycardia. The drugs tested included intravenous procainamide (15 mg/kg body weight), sotalol (160 to 480 mg/day) or the combination of quinidine gluconate (972 to 1,944 mg/day) and mexiletine (450 mg/day).

We retrospectively applied the ESVEM criteria for prediction of drug efficacy based on electrophysiologic testing to each follow-up study. We compared the drug efficacy predictions of the standard protocol with those of the ESVEM protocol. Furthermore, we determined whether differences in the efficacy predictions of the two protocols depended on the drug tested.

Statistics. Comparisons of drug trial results using the standard and ESVEM protocols were made using a chi-square analysis.

Results

The 125 patients underwent 176 follow-up electrophysiologic studies that were performed to determine the efficacy of antiarrhythmic drugs. Fifty-four drug trials were conducted with sotalol; 73 were conducted with procainamide, and 49 were conducted with the combination of quinidine gluconate and mexiletine.

During the baseline electrophysiologic study, ventricular tachycardia was induced with one extrastimulus in 15 patients, with two extrastimuli in 59 patients and with three extrastimuli in 51 patients. In six instances during reinduction at baseline, more extrastimuli were necessary to induce ventricular tachycardia. These baseline studies were classified according to the highest number of extrastimuli used to induce the ventricular tachycardia.

Fifty-four patients were tested during sotalol therapy using the standard protocol. Sotalol prevented induction of ventricular tachycardia in 14 (26%) of 54 patients. In six patients, ventricular tachycardia was induced with three extrastimuli during sotalol therapy, whereas it had been induced with one or two extrastimuli during the baseline study. Thus, the ESVEM protocol predicted sotalol efficacy in 20 patients (37%), whereas the standard protocol predicted the drug to be effective in only 14 (26%).

Seventy-three patients were tested during procainamide therapy using the standard protocol. Procainamide prevented induction of ventricular tachycardia in 7 (10%) of 73 patients. In seven patients, ventricular tachycardia was induced with three extrastimuli during procainamide therapy, whereas it had been induced with one or two extrastimuli during the baseline study. Thus, the ESVEM protocol predicted procainamide efficacy in 14 patients (19%), whereas the standard protocol predicted the drug to be effective in 7 (10%).

Forty-nine patients were tested during quinidine gluconate and mexiletine administration using the standard protocol. Quinidine gluconate and mexiletine prevented induction of ventricular tachycardia in only 1 (2%) of 49 patients. In six patients, ventricular tachycardia was induced with three extrastimuli during quinidine gluconate and mexiletine therapy, whereas it had been induced with one or two extrastimuli during the baseline study. Thus, the ESVEM protocol predicted quinidine gluconate and mexiletine efficacy in seven patients (14%), whereas the standard protocol predicted the drug combination to be effective in only one (2%).

Overall, the ESVEM protocol classified 41 (23%) of 176 drug trials as predicting efficacy, and the standard protocol classified 22 (12.5%) of 176 drug trials as predicting efficacy ($p < 0.05$). Thus, 19 of 143 drug trial results were discordant. All standard protocol drug trials predictive of failure were concordant with the ESVEM protocol predictions of failure. The overall discordance rate among trials was relatively constant among the different drugs: 6 (11%) of 54 for sotalol, 7 (10%) of 73 for procainamide and 6 (12%) of 49 for quinidine/mexiletine ($p = NS$) (Table 1). However, the discordance rate in trials with efficacy predictions was different among the three antiarrhythmic drug therapies tested. The discordant rate for sotalol efficacy prediction (30% [6 of 20]) was lower than that for the other drugs (procainamide or the combination of quinidine gluconate and mexiletine) tested (62% [13 of 21]) ($p < 0.05$) (Table 2).

Thirteen of the 14 patients in whom ventricular tachycardia induction was suppressed by sotalol using the standard protocol received the drug long term. In one patient the drug was discontinued before hospital discharge because of side effects.

Table 1. Results of 176 Electrophysiologic Trials in 125 Patients Undergoing Drug Testing to Suppress Ventricular Tachycardia Induction*

Drug Trial	No. (%) of Trials With ESVEM Efficacy Prediction	No. (%) of Trials With Standard Efficacy Prediction	No. (%) of Trials Discordant Between ESVEM and Standard Protocol
Sotalol (n = 54)	20 (37%)	14 (26%)	6 (11%)
Procainamide (n = 73)	14 (19%)	7 (10%)	7 (10%)
Quinidine/mexiletine (n = 49)	7 (14%)	1 (2%)	6 (12%)

*The discordance rate did not vary significantly among the drugs tested.

The 13 other patients were followed up for a mean (±SD) of 29 ± 10 months. Two deaths occurred from congestive heart failure at 6 and 24 months. Two arrhythmia recurrences occurred at 22 and 36 months. One recurrence, syncope, occurred in a patient who had discontinued sotalol therapy 2 weeks before the episode. Since that event, this patient has been asymptomatic for an additional 14 months while taking sotalol. The other patient with an arrhythmia recurrence had documented sustained ventricular tachycardia. This patient had a cardioverter-defibrillator implanted and continued to receive sotalol. Since implantation, this patient has been without device discharge over a 9-month period. The remaining nine patients were free of symptoms.

Discussion

This study may, in part, explain the ESVEM finding that long-term outcome was better in patients assigned to sotalol therapy rather than to other antiarrhythmic drugs despite equivalent efficacy predictions. In the present study, the ESVEM programmed stimulation protocol predicted drug efficacy more often than did the standard protocol (41 [23%] of 176 vs. 22 [12.5%] of 176, respectively). The ESVEM programmed stimulation protocol predicted efficacy for 19 drug trials that were classified as ineffective by the standard protocol. Overall discordant efficacy predictions between the standard and ESVEM protocol were equally likely to occur regardless of the antiarrhythmic drug tested (6 of 49 for quinidine/mexiletine, 7 of 73 for procainamide or 6 of 54 for sotalol). However, despite an overall discordance rate that was similar for all drugs, the discordance rate among trials only predictive of efficacy varied among the drugs. When a drug was predicted more likely to be effective, the discordant trials became a smaller portion of the ESVEM trials predicting efficacy (6 of 20 for sotalol vs. 7 of 14 for procainamide and 6 of 7 for quinidine/mexiletine).

Table 2. Potential Misclassifications*

Drug Trial	No. (%) of Trials Discordant Between ESVEM and Standard Protocol	No. (%) of Trials With ESVEM Efficacy Prediction	No. (%) of Discordant Trials/ESVEM-Predicted Efficacy Trials
Sotalol (n = 54)	6 (11%)	20 (37%)	6 of 20 (30%)
Procainamide (n = 73)	7 (10%)	14 (19%)	7 of 14 (50%)
Quinidine/mexiletine (n = 49)	6 (12%)	7 (14%)	6 of 7 (86%)

*If the discordant trials were misclassifications, then the misclassifications would be proportionately lower among patients assigned the higher predicted efficacy drug, sotalol, and proportionately higher among patients assigned the lower predicted efficacy drugs, procainamide or quinidine/mexiletine (30% [6 of 20] vs. 62% [13 of 21], $p \leq 0.05$).

If the discordant efficacy predictions were misclassifications of drug efficacy by the ESVEM protocol, then patients assigned to a drug with a lower overall efficacy prediction rate might be more likely to experience an arrhythmia recurrence. Thus, in the ESVEM trial, the programmed stimulation protocol may have correctly predicted efficacy in a higher proportion of patients who received sotalol than those who received other antiarrhythmic drugs. Therefore, long-term outcome in patients who received sotalol may have been better because the protocol predicted efficacy better in those patients rather than because of an inherent drug effect not predicted by electrophysiologic study.

Previous studies. The use of up to three ventricular extrastimuli during every follow-up electrophysiologic study was not standard clinical practice when the ESVEM trial was designed. At that time, many investigators advocated using only two ventricular extrastimuli during follow-up electrophysiologic studies if one or two extrastimuli had induced ventricular tachycardia during the baseline study. Swerdlow et al. (9) showed no difference in arrhythmia-free survival between patients who underwent a protocol similar to ESVEM and those who underwent a protocol similar to the standard protocol. However, the short follow-up period and differences in the size of the two patient groups limit the clinical usefulness of the study.

The results of the present study may be consistent with previous studies (4,5,7,10) that showed that the number of extrastimuli required to reinduce ventricular tachycardia can vary both from day to day and within a single electrophysiologic study. Thus, ventricular tachycardia induced with two extrastimuli might be induced with three extrastimuli at another time. Therefore, we and other investigators (6,7) advocate using up to three extrastimuli during all follow-up electrophysiologic studies regardless of the number of extrastimuli required to induce ventricular tachycardia during the baseline study.

Long-term follow-up. The long-term follow-up of the 14 patients in whom ventricular tachycardia was noninducible during sotalol therapy was similar to the experience of other investigators (2). In our series, sotalol was discontinued because of side effects in one patient; two patients died of refractory congestive heart failure; and two patients had

nonfatal arrhythmia recurrences. Importantly, a sudden death did not occur. Direct comparison of these patients with those assigned to receive sotalol in the ESVEM trial is difficult. The ESVEM trial was a rigorous prospective study. Our long-term data are complete but retrospective.

Study limitations. In the present study, because we could not determine long-term outcome in discordantly classified patients, we cannot state with any certainty that the ESVEM protocol overestimated drug efficacy. We can only speculate that many patients with arrhythmia recurrences in the ESVEM trial might have had ventricular tachycardia induced at the follow-up electrophysiologic study had three extrastimuli been used. The superior long-term follow-up in patients assigned to receive sotalol in the ESVEM trial is only consistent with the discordance findings between the two stimulation protocols. However, several studies (11,12) have shown that programmed stimulation protocols should utilize at least up to three extrastimuli to remain both sensitive and specific. Thus, many investigators (6) now advocate using up to three extrastimuli at each antiarrhythmic electrophysiologic study regardless of the number of extrastimuli necessary to induce ventricular tachycardia during the baseline study.

The comparisons of the discordant rate of sotalol (6 of 20) with the discordant rate of other drugs (13 of 21) are based on small numbers of patients. The statistical significance is borderline, and further studies may be necessary to confirm these data.

In the present study, intravenous procainamide and the drug combination of oral quinidine/mexiletine were compared with oral sotalol. In the ESVEM trial, different drugs were compared with sotalol. However, the potential bias in the ESVEM long-term follow-up data appears dependent on the suppression rate of ventricular tachycardia induction at electrophysiologic study and not the specific drug tested. On the basis of recent studies (1–3), sotalol appears to have a higher suppression rate of ventricular tachycardia induction than conventional antiarrhythmic agents. Therefore, as supported by our data, if ~10% of all drug trials, regardless of the drug tested, are discordant when comparing a standard protocol with an ESVEM protocol, the drug or drug combination with a lower suppression rate of ventricular tachycardia induction will have a higher proportion of discordantly classified patients. Because each of the drugs used in the ESVEM trial had a lower suppression rate of ventricular tachycardia induction at electrophysiologic study than sotalol, it follows that sotalol's superior long-term follow-up may have resulted from a more accurate classification at initial electrophysiologic testing.

Conclusions. In the present study, as was the case in the ESVEM trial, sotalol suppressed induction of ventricular tachycardia more often that the other drugs tested. The ESVEM programmed stimulation protocol predicted drug efficacy more often than the standard protocol (23% [41 of 176] vs. 12.5% [22 of 176]). A constant overall discordant rate (10% to 12%) between the ESVEM and standard protocols occurred regardless of drug tested. However, the proportion of discordant trials with positive efficacy predictions was greater for drugs with lower overall efficacy prediction rates (procainamide and quinidine/mexiletine, 62% [13 of 21]) than for sotalol (30% [6 of 20]).

We must emphasize that although it is a logical extrapolation of our data, the superior long-term follow-up in patients assigned to receive sotalol in the ESVEM trial only indirectly supports our hypotheses. To verify that the patients with arrhythmia recurrences were the patients discordantly classified by the ESVEM protocol, a randomized trial comparing the long-term results of drug therapy using the ESVEM and standard protocols would be necessary.

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