ECG Lead aVR Versus QRS Interval in Predicting Seizures and Arrhythmias in Acute Tricyclic Antidepressant Toxicity

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Study objective: To compare the value of ECG measurements from lead aVR with the QRS-interval duration in predicting seizures and ventricular arrhythmias due to acute tricyclic antidepressant (TCA) toxicity.

Design: Prospective cohort series of referral calls from hospitals to a regional poison control center.

Participants: Seventy-nine patients (mean age, 30±15 years) who presented within 24 hours of ingestion. Seizures occurred in 16 patients (20%) and ventricular arrhythmias in 5 (6%).

Interventions: The amplitude of the terminal R wave in lead aVR (R_{aVR}), the R-wave/S-wave ratio in lead aVR (R/S_{aVR}), and the maximal limb-lead QRS interval were measured on the initial ECG.

Results: R_{aVR} was greater in those patients who had seizures or arrhythmias than in those who did not (4.4 versus 1.8 mm, $P<.001$), as was R/S_{aVR} (1.4 versus .5, $P<.001$). The sensitivity of an R_{aVR} of 3 mm or more was 81% and that of an R/S_{aVR} of .7 or more was 75%, compared with 82% for QRS intervals greater than 100 milliseconds. The positive predictive value (PPV) of an R_{aVR} of 3 mm or more was 43% and that of the R/S_{aVR} of .7 or more 46%, compared with a PPV for QRS interval of 100 milliseconds or more of 35%. Multiple logistic-regression analysis demonstrated that an R_{aVR} of 3 mm or more was the only ECG variable that significantly predicted seizures and arrhythmias (OR, 6.9 [95% CI, 1.2 to 40], $P=.03$).

Conclusion: R_{aVR} and R/S_{aVR} were greater in patients in whom seizures or arrhythmias developed after an acute TCA overdose. R_{aVR} of 3 mm or more was the only ECG variable that significantly predicted these adverse outcomes.

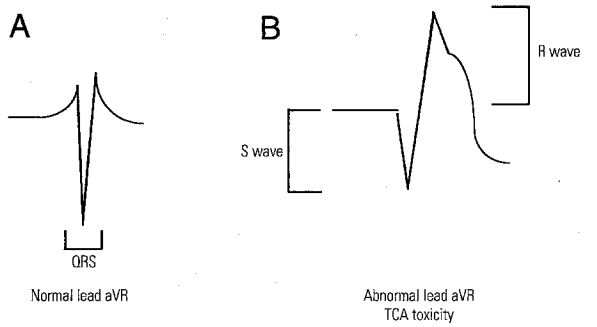
[Liebelt EL, Francis PD, Woolf AD: ECG lead aVR versus QRS interval in predicting seizures and arrhythmias in acute tricyclic antidepressant toxicity. *Ann Emerg Med* August 1995;26:195-201.]

INTRODUCTION

Tricyclic antidepressants (TCAs) are a leading cause of death in poisonings involving pharmaceutical agents in the United States.[1] Seizures and ventricular arrhythmias account for significant morbidity and mortality associated with serious TCA overdose in the first several hours of hospitalization. Decisions about treatment and patient disposition must frequently be made in the emergency department without the benefit of toxicology screen results or knowledge of serum TCA levels. The ECG is a convenient tool that can provide important diagnostic information in assessing patients after TCA overdose.[2-4]

The QRS-interval duration is frequently used by clinicians in their evaluation of patients with TCA poisoning. Boehnert and Lovejoy[2] reported that QRS intervals of 100 milliseconds or longer predicted seizures and ventricular arrhythmias. A terminal 40-millisecond frontal plane QRS axis between 120 and 270 degrees has been associated with TCA toxicity[3] and in one study[4] was a more sensitive indicator of general toxicity than the QRS interval alone. However, the terminal 40-millisecond frontal plane QRS axis is not easily measured in the absence of specialized computer-assisted analysis, limiting its usefulness. The objective of this study was to compare ECG measurements from lead aVR with QRS-interval duration alone as predictors of seizures and ventricular arrhythmias due to acute TCA toxicity.

Figure 1.
A, Normal QRS interval in lead aVR; B, an abnormal QRS interval as it appears in a patient with severe TCA poisoning.



R_{aVR} was measured as the maximal height in millimeters of the terminal upward deflection in the QRS complex, with the PQ segment used as the baseline. The S wave was measured in millimeters as the depth of the initial downward deflection.

MATERIALS AND METHODS

We conducted a prospective, nonconsecutive cohort study of patients with history of acute TCA overdose using calls made to the Massachusetts Poison Control System between April 23, 1992, and May 24, 1993. The system received approximately 44,000 calls in 1992.

Shortly after the initial call to the poison center, the consultant/investigator contacted the referring hospital to offer information on treatment and to collect information. Inclusion criteria were (1) suspected or known ingestion of a TCA, (2) a copy of the initial ECG from presentation, (3) an ECG obtained before the development of seizures or arrhythmias, (4) an ECG obtained before administration of sodium bicarbonate or other medications, (5) TCA ingestion in the 24 hours preceding the call (estimated on the basis of history from the patient, family, or friends), (6) confirmation of TCA ingestion by means of qualitative or quantitative analysis, (7) serum screening or combined serum and urine toxicology testing to distinguish between single-drug overdose (TCA only) and polydrug overdose (TCA and a drug of another class), and (8) lack of history or suspicion of ingestion of a concomitant cardiotropic agent (overdose or therapeutic).

We used a standardized data sheet to record information including age; sex; time of ingestion, if known; total dose of TCA, if known; other medications; history of heart disease; and time of presentation. Follow-up information on decontamination measures, blood and urine toxicology screen results, serum TCA levels, complications, and other management was collected at 4 hours, 24 hours, and daily until medical discharge.

A blinded cardiologist manually measured three variables on the initial standard ECG: the amplitude of the terminal R wave in lead aVR (R_{aVR}), the R-wave/S-wave ratio in lead aVR (R/S_{aVR}), and the maximal limb-lead QRS interval. Figure 1 illustrates a normal QRS complex in lead aVR and an abnormal QRS complex in a patient with severe TCA poisoning. Low voltages were found in some patients, diminishing the absolute value of the R wave; therefore an R/S_{aVR} was calculated. The ECG parameters were compared between patients in whom seizures or ventricular arrhythmias developed and those in whom they did not. Ventricular arrhythmias were defined as ventricular tachycardia, ventricular fibrillation, multifocal premature ventricular contractions, idioventricular rhythm, bigeminy, trigeminy, or asystole.

We analyzed normally distributed continuous variables with two-tailed Student *t* tests, categorical values with χ^2 analysis, and nonnormally distributed data with the Mann-Whitney U test by means of a statistical program

(SPSS/PC+ V4.0).[5] Data are expressed as mean±SD, unless otherwise noted. Sensitivity, specificity, and positive predictive values (PPVs) and negative predictive values (NPVs) were calculated according to standard methods. We performed forward stepwise multiple logistic-regression analysis to identify predictors of seizures and arrhythmias with the STATA software program.[6] ORs with 95% CIs were computed. Receiver-operator characteristic curves (ROCs) were generated for R_{aVR} and QRS interval.[7] Areas under the curve, SEs, and comparisons of the two areas were computed with the ROC analyzer program.[8] For all analyses an α level of .05 was used to demonstrate statistical significance. The study was approved by the investigational review board of Boston Children's Hospital.

RESULTS

Eighty-seven patients with a mean age of 30±15 years (range, 1.2 to 87 years) met all inclusion criteria. Fifty-eight (67%) of subjects were female. Patients had ingested the following TCAs: amitriptyline, 43; nortriptyline, 10; imipramine, 12; doxepin, 10; desipramine, 7; clomipramine, 4; and an unidentified TCA, 1. All patients underwent gastrointestinal decontamination and received activated charcoal in the emergency department. Comprehensive toxicologic testing identified a TCA only in 45 patients and a TCA and at least one other drug in 42 patients. These other drugs included ethanol, 14; benzodiazepines, 8; salicylate, 4; acetaminophen, 3; cocaine, 3; opiates, 3; diphenhydramine, 3; fluoxetine, 2; lithium (at therapeutic levels), 2; phenothiazine, 1; carbamazepine, 1; and cyclobenzaprine, 1. Because we could not determine whether drugs such as cocaine, benzodiazepines, and carbamazepine might have caused or conferred protection against seizures, we excluded eight patients: one with cocaine, diphenhydramine and carbamazepine on toxicologic testing in whom seizures developed and seven with benzodiazepines on urine assays who did not have seizures. The eighth patient with a benzodiazepine on urine assay had a TCA level of 0 and was kept in the control group. The remaining patients with cocaine, diphenhydramine, or phenothiazine in their urine screens did not have seizures or arrhythmias and were kept in the control group. The remaining 79 patients were used as the population for analysis.

Of the 79 patients, 29 (37%) were comatose on presentation, 24 (30%) lethargic, 13 (17%) agitated or delirious, and 13 (17%) asymptomatic. The interval from ingestion to presentation was known in 53 patients (2.7±2.8 hours; range, .17 to 13.5 hours). Seventy-seven patients were admitted to the hospital. They had continuous heart monitoring in the ED and for at least the first 24 hours of hospitalization. Two asymptomatic patients with TCA levels of 0 were discharged home from the ED after several hours of heart monitoring.

Of the 79 subjects, 54 had three or more ECGs, whereas 25 had only one or two ECGs. Of the 54 patients with multiple ECGs, 15 had normal initial ECGs that remained normal and 39 had initial abnormal ECGs (defined as QRS interval of 100 milliseconds or more, R_{aVR} of 3 mm or more, R/S_{aVR} of .7 or more, or all three). Follow-up ECGs showed resolution of one or more of these abnormalities.

Sixteen patients (20%) had documented generalized tonic-clonic seizures within 3 hours of presentation. Two patients in whom seizures developed had also ingested ethanol. Ventricular arrhythmias occurred in five patients (6%): ventricular tachycardia (n=4), asystole (n=2), and multiple unifocal premature ventricular contractions (PVCs) and couplets (n=1). All patients with ventricular arrhythmias also had seizures, except one child with multiple unifocal PVCs (up to 60/minute) and couplets, which resolved. These 17 patients were analyzed as a subgroup: patients with seizures or arrhythmias. One 15-year-old patient died of complications of adult respiratory distress syndrome after 9 days (overall mortality, 1.2%).

The clinical characteristics of patients with seizures or arrhythmias and those who did not were not different, except that the serum TCA concentration on presentation was higher in patients with seizures or arrhythmias (Table 1).

Table 1.
Clinical characteristics.

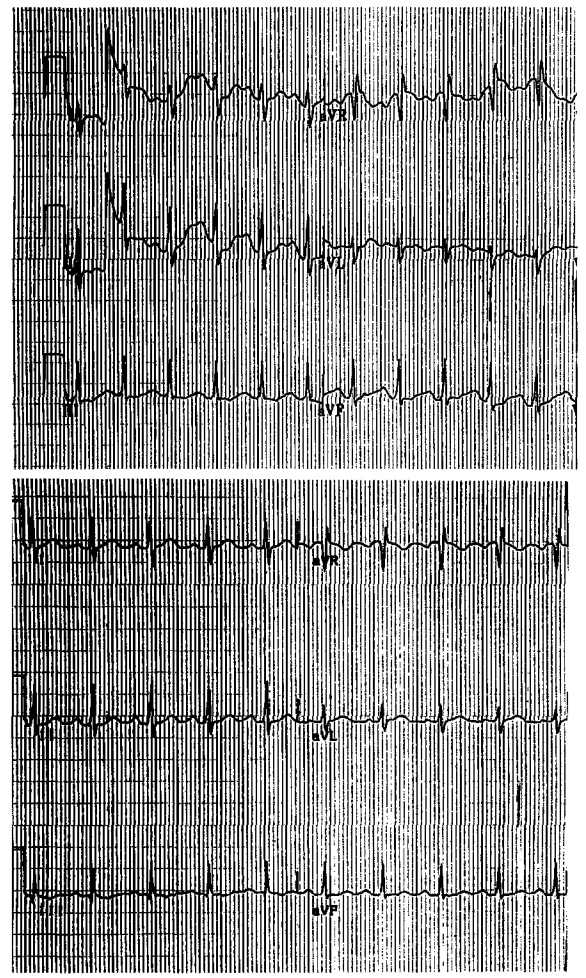
Characteristics	Seizure or Arrhythmia (n=17)	No Seizure or Arrhythmia (n=62)	P
Age (yr)*	26±12 (4-51)	31±16 (1.2-87)	NS†
Male/female	7:10	20:42	NS‡
Time from ingestion to ED arrival (hr)*	3.2±3.8 (.8-12.5)§	2.6±2.6 (.2-12)¶	NS#
Single-drug (TCA) on toxicology screen	12 (71%)	33 (53%)	NS‡
TCA serum concentration (ng/mL)*	2,025±1,640 (477-5,600)**	522±501 (0-2,412)††	<.001#

*Data expressed as mean±SD (range).
†Unpaired, two-tailed Student *t* test.
‡χ^2 test
§n=10.
¶n=43.
#Mann-Whitney U test.
**n=14.
††n=48.

R_{aVR}, R/S_{aVR}, and mean QRS-interval duration were all significantly greater in patients with seizures or arrhythmias (Table 2). The ECG heart rate was also significantly higher, but there was no significant difference in presenting systolic blood pressure.

Figure 2A shows the initial ECG of a patient, comatose on presentation $1\frac{1}{2}$ hours after taking 2,000 mg of imipramine, who had generalized tonic-clonic seizures.

Figure 2.
A, Initial ECG of a 19-year-old patient who presented comatose $1\frac{1}{2}$ hours after taking 2,000 mg of imipramine and had generalized tonic-clonic seizures. B, ECG from the same patient 33 hours later.



A, This ECG, performed before the onset of seizures, shows an R_{aVR} of 5 mm and an R/S_{aVR} of .8; the QRS interval was 95 milliseconds. The patient required intubation and received sodium bicarbonate, benzodiazepines, and phenytoin.

B, This ECG shows an R_{aVR} of 3.5 mm, an R/S_{aVR} of .5, and a QRS interval of 90 milliseconds.

The ECG of the same patient 33 hours later demonstrated resolution of the ECG effects (Figure 2B).

Four patients were younger than 12 years (range, 15 months to 5 years). Data analysis was repeated after omission of these patients. There were no significant differences in any of the ECG variables or other demographic analyses. We found no significant differences when data were stratified by sex.

We also reanalyzed the data including only the 50 patients who presented without coma (agitated, delirious, lethargic, or asymptomatic). Five patients had seizures, and one patient had an arrhythmia. R_{aVR}, R/S_{aVR}, and QRS-interval duration were all greater in these patients than in patients who did not have seizures or arrhythmias.

Parameters with ideal diagnostic accuracy lie in the upper left corner of the ROC curve, with sensitivity and specificity both equaling 1.0 (Figure 3). R_{aVR}s of 3 mm or more had a sensitivity of 81% and specificity of 73%, and those 5 mm or greater had a sensitivity of 50% and specificity of 97% in identifying patients in whom seizures or arrhythmias developed. These values are in contrast to QRS intervals of 100 milliseconds or more, which had a sensitivity of 82% and specificity of 58%, and that of 120 milliseconds or more, which had a sensitivity of 59% and specificity of 87%.

In 13 of 30 patients (43%) with R_{aVR}s greater than or equal to 3 mm and 12 of 26 patients (46%) with R/S_{aVR}s greater than or equal to .7, seizures or arrhythmias developed. The PPVs of both of these ECG parameters are greater than that for a QRS interval duration of 100 milliseconds or more (Table 3). The PPV of an R_{aVR} of 5 mm or more was 80% (8 of 10 patients). The NPVs were similar for all ECG variables.

A forward stepwise multiple logistic-regression model was constructed with age, single (TCA only) versus polydrug ingestion, R_{aVR}, R/S_{aVR}, and QRS interval as the independent variables and seizures or arrhythmias as the dependent outcome variable. A relationship was found

Table 2.
ECG parameters.

Features	Seizure or Arrhythmia (n=17)	No Seizure or Arrhythmia (n=62)	*P*
R_{aVR} (mm)	4.4±2.3 (.5-9.0)	1.8±1.4 (.0-5.5)	<.001*
R/S_{aVR}	1.4±1.2 (.0-4.5)	.5±.7 (.0-5.0)	<.001†
QRS interval (msec)	147±57 (60-260)	96±28 (60-260)	.002*

Data expressed as mean±SD (range).
*Unpaired Student *t* test.
†Mann-Whitney U test.

between R_{aVR} and the risk of seizures or arrhythmias (OR, 2.3; 95% CI, 1.5 to 3.5; $P<.001$). No other variable was significantly associated with this outcome. A second model was analyzed that stratified these variables: single (TCA only) versus polydrug ingestion, TCA concentration of 1,000 ng/mL or more versus concentration of less than 1,000 ng/mL, R_{aVR} 3 mm or more versus R_{aVR} less than 3 mm, R/S_{aVR} of .7 or more versus R/S_{aVR} less than .7, and QRS interval of 100 milliseconds or more versus interval less than 100 milliseconds as the independent variables and seizures/arrhythmias as the dependent outcome variable. R_{aVR} of 3 mm or greater was a significant predictor of seizures and arrhythmias (OR, 6.9; 95% CI, 1.2 to 40.0; $P=.03$), as was TCA concentration of 1,000 ng/mL or more (OR, 9.5; 95% CI, 2.0 to 46; $P=.005$). There was no colinearity between R_{aVR} and R/S_{aVR} when the data were analyzed with logistic regression. This finding suggests that the S wave had an independent effect. The QRS interval was not a significant predictor.

DISCUSSION

The TCAs have quinidine-like effects on the distal conduction system of the heart. They inhibit the rapid inward movement of sodium ions in the cardiac Purkinje cells during depolarization, causing a decrease in conduction velocity, prolonging the action potential, and depressing His-Purkinje conduction.[9-11] These effects are manifested on the ECG as conduction delays—specifically, QRS interval prolongation, reentry ventricular arrhythmias, and asystole.

Seizures and ventricular arrhythmias were chosen as outcome measures in our study. There appears to be a relationship between the central nervous system (CNS) and cardiac manifestations of TCA poisoning. Conduction changes on the ECG reflect the pathophysiology of TCA poisoning at the cellular level. Thus it is logical that these electrical current changes would also occur in the CNS, resulting in seizures. We did not use mental status on presentation as an outcome measure because this measurement is not as specific for TCA poisoning. Mental status changes may not be a good predictor of either outcome; there have been reports of abrupt onset of seizures, malignant arrhythmias, and cardiovascular collapse without warning.[12]

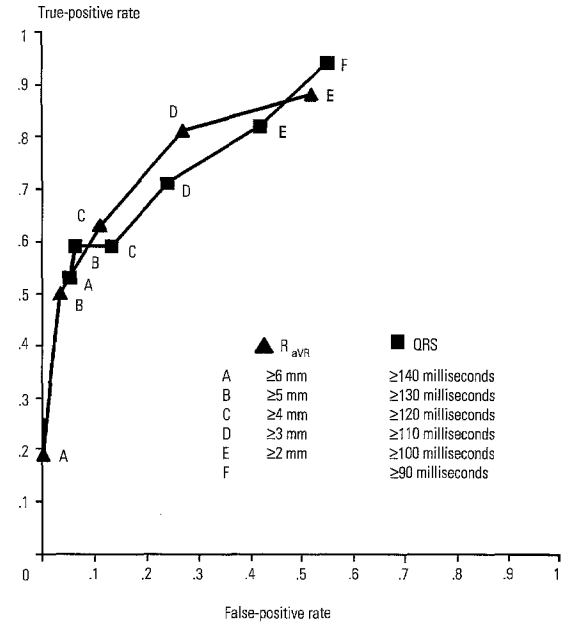
Boehnert and Lovejoy[2] showed prospectively that a QRS interval of 100 milliseconds or longer predicted seizures in 33% of their study patients and ventricular arrhythmias in 14%. However, a subsequent retrospective study of 102 patients did not find a significant relationship between QRS-interval duration and the occurrence of seizures or ventricular arrhythmias.[13] Our study provides support for the findings of Boehnert and Lovejoy in that the QRS interval was longer in patients in whom seizures or arrhythmias developed. However, we found that a QRS interval of 100 milliseconds or more was not an independent predictor of seizures or arrhythmias.

Niemann and associates[3] reported that a terminal QRS vector of 130 to 270 degrees discriminated between 11 patients with positive toxicology screens for TCAs and 14 patients with negative screens. They postulated that the distal conduction system of the right side of the heart is more susceptible to TCAs and that the rightward shift of the QRS axis reflects aberrant intraventricular conduction.

Table 3.
Value of ECG parameters in predicting seizures and arrhythmias.

ECG Parameters	PPV	NPV
R_{aVR} 3 mm or more	43% (13 of 30)	94% (45 of 48)
R/S_{aVR} .7 or more	46% (12 of 26)	92% (48 of 52)
QRS interval 100 msec or more	35% (14 of 40)	92% (36 of 39)

Figure 3.
ROC for R_{aVR}, superimposed on a curve for QRS interval.



Area under the R_{aVR} curve (.68) was greater than that of the QRS curve (.65), but not statistically significantly so ($P=.37$).

In a retrospective study of 78 patients, Wolfe et al[4] found that a terminal 40-millisecond frontal plane axis of 120 to 270 degrees was a more sensitive indicator of TCA toxicity than the QRS interval. We used this information to hypothesize that one could use easily quantifiable measurements in lead aVR to predict toxicity because this lead is used in the measurement of the terminal 40-millisecond frontal-plane axis.

R_{aVR} and R/S_{aVR} reflect the rightward shift of the terminal QRS axis in patients with TCA toxicity. In this study, both of these ECG parameters were significantly greater in patients in whom seizures, arrhythmias, or both developed; neither has been previously reported as a predictor of TCA toxicity. The ROC curves were similar for R_{aVR} and QRS interval, suggesting that their usefulness in predicting seizures and arrhythmias is similar. Compared with that of an R_{aVR} of 3 mm or more, the sensitivity of a QRS interval of 100 milliseconds or more was similar (82% versus 81%), yet the specificity was lower (58% versus 73%). In our population, the PPVs of R_{aVR}s of 3 mm or more and 5 mm or more and of R/S_{aVR} of .7 or more were greater than that of a QRS-interval duration of 100 milliseconds or more, although all parameters had similar high NPVs. Taking into account potential confounding variables of age and single (TCA alone) versus polydrug ingestion, R_{aVR} was the only ECG variable that was significantly associated with seizures or arrhythmias on logistic-regression analysis.

As shown in Figure 2, this pattern of increased R-wave amplitude was seen in lead aVR in the presenting ECG and decreased over time during hospitalization. The ECG shows an initial QRS interval of less than 100 milliseconds but an R_{aVR} of 5 mm and an R/S_{aVR} of .8; seizures later developed in this patient.

Published tables report normal mean values and ranges in children and adults for R-wave and S-wave amplitudes in lead aVR, QRS intervals, and frontal plane QRS axis.[14-16] The ECG of a $1^1/_2$-year- old child is closer to that of an adult than to that of a newborn. Furthermore, age was not a confounding variable in the regression analysis. There are no reported values of R/S_{aVR}.

We postulate, on the basis of our results, as well as the finding of a right bundle-branch pattern in many patients with serious TCA overdoses[17,18], that these patterns are due to the longer refractory period of the right bundle of the conduction pathway, which makes the right side of the heart more vulnerable to conduction delays. These patterns may also be due to the synergism of TCAs' anticholinergic properties and sodium ion–channel blockade, which causes rate-dependent conduction slowing.[19]

We included all patients with known or suspected TCA overdose within a 24-hour period. Although retrospective studies have shown most seizures to occur within several hours of ingestion, the spectrum of clinical complications is unpredictable. Seizures have been reported 7 and 14 hours after admission in decontaminated patients after TCA ingestion (which may have been masked by other, concomitant ingestions).[12] Unpredictable complications may be due to many factors, including drug tolerance, interindividual variation, and concomitant ingestion of drugs that may delay or precipitate the onset of seizures or arrhythmias. Furthermore, the exact time of drug ingestion is rarely known, especially in the suicidal or depressed patient, making this variable unreliable.

This study had several limitations. First, our study population was a nonconsecutive sample derived from calls to a regional poison center only, creating a selection bias. The prevalence of seizures and arrhythmias in our sample may not reflect the prevalence in all patients with TCA overdoses, thereby limiting the generalizability of the data. The PPV of the ECG parameters will differ depending on the prevalence of seizures and ventricular arrhythmias in the study population. Although the data may be biased toward sicker patients, our purpose was to predict serious toxicity. Second, ECGs were not obtained on all potential subjects during the study period, making our series nonconsecutive. Third, the interval from ingestion to the first ECG was different for each patient. This variable may have been a confounder in our outcome measures. However, adding this variable to our model would have significantly decreased our number of subjects because it was not known in 26 subjects. This initial ECG was the one on which the clinicians were basing their decisions. Fourth, there were no preoverdose baseline ECGs for comparison; however, it can generally be assumed that the abnormalities observed were the result of TCA toxicity because of their temporal relationships to TCA overdose and their subsequent resolution.

The ECG can be an easy-to-use, helpful tool in predicting seizures and arrhythmias. Certain ECG parameters can help predict cardiac and neurologic complications. However, ECG parameters alone are not ideal and should be used in conjunction with the patient's clinical presentation, history, and course during the first hours in decision-making with regard to disposition and interventions. We are developing a scoring system that includes signs and symptoms, as well as different ECG parameters, in predicting clinical course and outcome.

CONCLUSION

In conclusion, R_{aVR} and R/S_{aVR} are both significantly greater in patients in whom seizures or arrhythmias subsequently developed. These two ECG parameters were better predictors than the QRS-interval duration. An R_{aVR} of 3 mm or more was the only ECG predictor of seizures or arrhythmias. These ECG parameters are readily available and easily measured such that the physician can make decisions about patient management when dealing with a suspected TCA overdose.

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