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# Amiodarone or Procainamide for the Termination of Sustained Stable Ventricular Tachycardia: An Historical Multicenter Comparison

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## Abstract

***Objectives:*** The objective was to compare the effectiveness of intravenous (IV) procainamide and amiodarone for the termination of spontaneous stable sustained ventricular tachycardia (VT).

***Methods:*** A historical cohort study of consecutive adult patients with stable sustained VT treated with IV amiodarone or procainamide was performed at four urban hospitals. Patients were identified for enrollment by admissions for VT and treatment with the study agents in the emergency department (ED) from 1993 to 2008. The primary measured outcome was VT termination within 20 minutes of onset of study medicine infusion. A secondary effectiveness outcome was the ultimate need for electrical therapy to terminate the VT episode. Major adverse effects were tabulated, and blood pressure responses to medication infusions were compared.

***Results:*** There were 97 infusions of amiodarone or procainamide in 90 patients with VT, but the primary outcome was unknown after 14 infusions due to administration of another antidysrhythmic during the 20-minute observation period. The rates of VT termination were 25% (13/53) and 30% (9/30) for amiodarone and procainamide, respectively. The adjusted odds of termination with procainamide compared to amiodarone was 1.2 (95% confidence interval [CI] = 0.4 to 3.9). Ultimately, 35/66 amiodarone patients (53%, 95% CI = 40 to 65%) and 13/31 procainamide patients (42%, 95% CI = 25 to 61%) required electrical therapy for VT termination. Hypotension led to cessation of medicine infusion or immediate direct current cardioversion (DCCV) in 4/66 (6%, 95% CI = 2 to 15%) and 6/31 (19%, 95% CI = 7 to 37%) patients who received amiodarone and procainamide, respectively.

***Conclusions:*** Procainamide was not more effective than amiodarone for the termination of sustained VT, but the ability to detect a significant difference was limited by the study design and potential confounding. As used in practice, both agents were relatively ineffective and associated with clinically important proportions of patients with decreased blood pressure.

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**Keywords: tachycardia, ventricular; amiodarone; procainamide**

Sustained ventricular tachycardia (VT) is an uncommon but dangerous condition seen in emergency and critical care medicine. If the patient appears stable based on adequate vital organ perfusion, intravenous (IV) pharmacologic therapy to terminate the tachydysrhythmia may be initiated. Recent

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guidelines recommend amiodarone or procainamide, or lidocaine if the VT is thought to be related to ongoing myocardial ischemia.[1,2] Amiodarone terminates VT in only approximately 29% of patients, but it seems relatively safe.[3,4]

When administered at a rate of 50 to 100 mg/min up to a dose of 10 to 15 mg/kg, procainamide terminates VT in up to 80% to 90% of patients.[5,6] Procainamide may be more effective than amiodarone acutely due to faster onset of QT interval and myocardial refractory period prolongation with infusion.[7–10] The use of procainamide, however, has been tempered by adverse effects that also necessitate relatively slow IV loading of the agent. When infused at a rate of 50 mg/min, procainamide has been associated with a decrease in left ventricular function and blood pressure.[11,12] For this reason, the American Heart Association recommends an infusion rate of 20 mg/min to a total dose of 17 mg/kg.[1] Thus, a full loading dose for a 70-kg patient would require a 1-hour infusion. The proportion of patients with VT termination and the timing of this response with the recommended slower infusion protocol are unknown.

No direct comparison of the performance of amiodarone and procainamide for this indication has been reported. We hypothesized that, as used in clinical practice, procainamide is more effective than amiodarone for the termination of spontaneous sustained VT.

## METHODS

### Study Design

This report describes an historical cohort study of consecutive patients with spontaneous sustained VT treated with IV amiodarone or procainamide. Institutional review board approval with waiver of informed consent was obtained from all participating institutions.

### Study Setting and Population

This was a multicenter study performed at four urban hospitals in three cities (Table 1). Patients were primarily identified at their emergency department (ED) presentation, but the first administration of amiodarone or procainamide for each visit with adequate information for inclusion, beginning with treatment by emergency medical services (EMS) and ending in the inpatient hospital unit, was used. A variety of overlapping search criteria were used to identify cases depending primarily on the medical record documentation, storage, and search capabilities available at each facility (Table 1). Some patients treated with amiodarone were described in a previous report.[3] This study was performed concurrently with a study of the utility of adenosine for wide QRS complex tachycardia (WCT).[13] It is conceivable a patient may have received and been billed for adenosine in the ED and also have received amiodarone or procainamide either before ED arrival by EMS in the field or after leaving the ED in the cardiac care unit. For this reason, these patients were also eligible for inclusion in this study.

All cases in which a patient greater than 16 years old presented with spontaneous stable sustained WCT, and an order was written for at least 150 mg amiodarone IV infusion at a rate of at least 10 mg/min, or at least 500 mg procainamide infusion at a rate of at least 15 mg/min, were eligible for inclusion. If other medicines were administered prior to amiodarone or procainamide, the medicine, dose, time, and response, if any, were noted, and the patient remained eligible for inclusion. Patients were retained in the study if the amiodarone or procainamide infusion was stopped prior to completion due to tachydysrhythmia termination, electrical therapy, or adverse effects. For this study, the rhythm was considered stable if the treating physician elected to use pharmacologic therapy as the initial treatment. A sustained rhythm was defined as a continuous rhythm, or immediately recurrent VT after implantable cardioverter defibrillator (ICD) therapy, for at least 2 minutes. WCT was defined as a QRS width greater than or equal to 120 milliseconds and a heart rate of at least 120 beats/min.

Table 1
Enrollment Information

| Hospital | Location | Beginning Search Date | Ending Search Date | Search Criteria | Amiodarone Treatment | Procainamide Treatment |
|---|---|---|---|---|---|---|
| Massachusetts General Hospital | Boston, MA | October 1993 | January 2008 | A and B | 37 | 19 |
| Brigham and Women's Hospital | Boston, MA | January 1994 | October 2006 | A and B | 11 | 9 |
| Mount Auburn Hospital | Cambridge, MA | September 1996 | December 2006 | Digital text search of all ED physician charts for the consecutive letters ''VT,'' ''vent tach,'' 'aden,'' ''amio,'' or ''procain'' | 14 | 3 |
| SUNY Downstate Medical Center | Brooklyn, NY | July 1999 | February 2005 | A | 4 | 0 |
| Totals | | | | | 66 | 31 |

A = primary discharge diagnosis ''paroxysmal ventricular tachycardia,'' ICD-9 427.1. B = all ED patients with a pharmacy charge for intravenous adenosine, amiodarone, or procainamide.
VT = ventricular tachycardia.

Table 2
How Was the Diagnosis Proven?

| | Amiodarone, *n* (%) | Procainamide, *n* (%) |
|---|---|---|
| ECG with AV dissociation | 6 (9) | 6 (19) |
| ECG with fusion beats | 1 (2) | 0 (0) |
| ECG with VT with variable retrograde VA conduction | 2 (3) | 2 (6.5) |
| ICD interrogation with VT | 6 (9) | 2 (7) |
| ICD interrogation with VT and AV dissociation | 5 (8) | 0 (0) |
| EP study with tachydysrhythmia reproduced | 27 (41) | 11 (36) |
| EP study with tachydysrhythmia reproduced and AV dissociation | 4 (6) | 4 (13) |
| ECG criteria per cardiology team confirmed by investigators | 3 (5) | 2 (7) |
| ECG criteria per blinded electrophysiologist | 12 (18) | 4 (13) |

AV = atrioventricular; ECG = electrocardiogram; EP = electrophysiology; VA = ventriculoatrial; VT = ventricular tachycardia.

Patients were included if the WCT was proven to be VT. VT was proven using a hierarchy of evidence in descending order: electrocardiogram (ECG) evidence or review of the tachydysrhythmia from ICD recordings demonstrating atrioventricular dissociation or retrograde ventriculoatrial conduction consistent with VT, reproduction of the dysrhythmia during an EP study with evidence of a ventricular origin, ECG analysis by the treating cardiology team with clear evidence of VT confirmed by the investigators, or if necessary, ECG analysis using standard criteria by an electrophysiologist investigator blinded to all clinical data (Table 2).[14,15]

Patients who developed VT during resuscitation of cardiac arrest or were receiving ongoing vasopressor medication infusions were excluded, as were patients whose VT occurred via induction in the electrophysiology lab. If a patient was treated on multiple occasions, only the first event for which there was complete data was included. Patients who received both study medicines on the same or different occasions were included once in each study group.

### Study Protocol

Three unblinded investigators collected data using standardized abstraction forms following a prospectively written protocol. The principal investigator trained the other abstractors and reviewed all of the forms in periodic meetings. For variables noted multiple times on the chart, the first documented value was recorded. Unavailable information was documented as missing. Reliability of chart data abstraction was assessed using a fourth investigator who was blinded to the study hypothesis and data collected by the other abstracters. This investigator reviewed all available records at a single study site and completed an abbreviated abstraction form that included ordered and administered study medication doses and the primary and secondary study outcomes.

Patients' demographics, including age and sex, the date of the WCT presentation, and the hospital and hospital unit, were recorded. History of cardiac disease, including dysrhythmias, ICD implantation, congestive heart failure and most recent measured left ventricular ejection fraction (LVEF), coronary artery disease, myocardial infarction (MI), or coronary artery bypass grafting (CABG), was obtained from the medical record. Medications at presentation, including class I and III antidysrhythmics, beta blockers, and digoxin, were recorded.

The characteristics of the VT were recorded, including the duration of the dysrhythmia prior to treatment, if known, and all heart rate and blood pressure measurements from the onset of medical care until termination of the VT. The dose, duration of infusion, and timing of the study medicine and any preceding or subsequent antidysrhythmic treatments were noted. If the patient had an ICD, evidence of ICD therapy such as antitachycardia pacing or defibrillation before or during study medicine treatment based on symptoms, telemetry, or ICD interrogation were recorded. The order of treatment of the study medicine with respect to other antidysrhythmic treatments was recorded. For example, if procainamide was administered after another treatment (such as lidocaine) had been tried, then its order was second. Adenosine was not included in this ordering because, given its short 9-second half-life, it was unlikely to affect subsequent therapies. Because it is not a typical antidysrhythmic, magnesium was also excluded from this ordering. Instead, its use, including dosage and timing, was noted separately.

Symptoms of chest pain or shortness of breath, and physical signs including pulmonary rales and peripheral edema, were recorded. Measured patient weight and serum potassium, magnesium, and calcium were noted. ECG characteristics including heart rate, and QRS, QT, and QTc durations were taken from the automated recordings on the tracing with manual measurement and correction for any obviously incorrect readings.

Acute MI was diagnosed in association with the VT event if the patient demonstrated characteristic elevation of cardiac markers, and was diagnosed by the cardiology team caring for the patient. Any patient death during hospitalization and the reason for death was recorded.

### Outcome Measures

The primary outcome measurement was termination of the VT within 20 minutes of initiation of the amiodarone or procainamide infusion. Termination was defined as conversion to the patient's known or presumed usual heart rhythm (e.g., sinus, atrial fibrillation). If the dysrhythmia recurred within 5 minutes after termination, the treatment was considered unsuccessful.

Table 3
Patient Characteristics

| Study Medicine: VT Terminated: | Amiodarone Yes (*n* = 13) | Amiodarone No (*n* = 40) | Amiodarone Unknown (*n* = 13) |
|---|---|---|---|
| Demographics | | | |
| Age, yr (±SD) | 63.1 (18) | 66.0 (15) | 64.1 (17) |
| Sex, male, *n* (%) | 8 (62) | 31 (78) | 7 (54) |
| Mean year of study enrollment (1992 = 1) (±SD) | 13.2 (2.5) | 12.0 (2.3) | 13.3 (2.7) |
| Medical history, *n* (%) | | | |
| History of MI | 8 (62) | 28 (70) | 7 (54) |
| History of CABG | 3 (23) | 15 (38) | 3 (23) |
| Mean LVEF (±SD) | 42.4 (19) | 33.0 (12) | 38.5 (18) (*n* = 12) |
| LVEF ≤ 35% | 6 (46) | 26 (65) | 6/12 (50) |
| History of VT | 6 (46) | 23 (58) | 6 (46) |
| Medications, *n* (%) | | | |
| Antidysrhythmic (class I or III) | 1 (8) | 16 (40) | 4 (31) |
| Beta adrenergic blocker | 8 (62) | 22 (55) | 5 (39) |
| Digoxin | 3 (23) | 15 (38) | 4 (31) |
| History of ICD implant | 3 (23) | 19 (48) | 6 (46) |
| Recurrent VT despite ICD therapy before or during treatment | 2 (15) | 8 (20) | 5 (38) |
| History of present illness, *n* (%) | | | |
| Chest pain | 4/12 (33) | 10/39 (26) | 5 (39) |
| Shortness of breath | 3/12 (25) | 9/38 (24) | 1 (8) |
| Physical exam | | | |
| Heart rate (beats/min) (±SD) | 171 (30) | 159 (35) (*n* = 39) | 187 (27) (*n* = 12) |
| sBP (mm Hg) (±SD) | 103 (23) (*n* = 12) | 118 (23) (*n* = 39) | 117 (27) (*n* = 12) |
| Patient weight (kg) (±SD) | 81 (22) | 82 (17) | 81 (17) |
| Pulmonary rales, *n* (%) | 1 (8) | 8 (20) | 1 (8) |
| Lower extremity edema, *n* (%) | 2 (15) | 2 (5) | 1 (8) |
| Serum electrolytes (±SD) | | | |
| Potassium (mmol/L) | 4.2 (0.3) (*n* = 12) | 4.1 (0.7) | 3.9 (0.6) (*n* = 12) |
| Magnesium (mEq/L) | 1.7 (0.2) (*n* = 11) | 1.9 (0.4) (*n* = 36) | 1.9 (0.3) (*n* = 11) |
| Calcium (mg/dL) | 9.4 (0.8) (*n* = 12) | 9.2 (0.7) (*n* = 39) | 9.3 (0.8) (*n* = 12) |
| Treatment | | | |
| Dose (mg) (±SD) | 162 (42) | 161 (40) | 185 (66) |
| Dose per weight (mg/kg) (±SD) | 2.2 (0.8) | 2.0 (0.6) | 2.4 (1.0) |
| Infusion rate (mg/min)* (±SD) | 20 (15) (*n* = 6) | 14 (4) (*n* = 26) | 13 (3) (*n* = 3) |
| SIVP infusion, *n* (%) | 1 (8) | 2 (5) | 3 (23) |
| Order of treatment (±SD) | 1.5 (0.7) | 1.4 (0.5) | 1.6 (1.0) |
| Study medicine was initial treatment, *n* (%) | 8 (62) | 26 (65) | 8 (62) |
| Magnesium infused before or within 20 minutes after study medicine, *n* (%) | 1/12 (8) | 5 (13) | 2/12 (17) |
| Final therapy electrical, *n* (%) | 0 (0) | 27 (68) | 8 (62) |
| Outcome, *n* (%) | | | |
| Associated NSTEMI | 1 (8) | 1 (3) | 2 (15) |
| Associated STEMI | 1 (8) | 0 (0) | 0 (0) |

CABG = coronary artery bypass grafting; MI = myocardial infarction; LVEF = left ventricular ejection fraction; NSTEMI = non-ST elevation myocardial infarction; sBP = systolic blood pressure; SIVP = slow intravenous push; STEMI = ST-elevation myocardial infarction; VT= ventricular tachycardia.
*Infusions with rate unspecified or specified as slow intravenous push (SIVP) were treated as unknown.
Note: There are different ''n''specified in the table because some of the data points were not available for some patients.

If a different antidysrhythmic medicine was administered or direct current cardioversion (DCCV) was performed before dysrhythmia termination, but within 20 minutes of initiation of the study drug infusion, the response to amiodarone or procainamide was classified as ''unknown.'' If a study drug infusion was stopped due to an adverse effect such as hypotension prior to tachydysrhythmia termination, the treatment was considered unsuccessful. If multiple boluses of the study medication were administered, these were summed such that the total dose over the total infusion period, up to 20 minutes, was recorded. If an initial bolus was

| Procainamide Yes (*n* = 9) | Procainamide No (*n* = 21) | Procainamide Unknown (*n* = 1) | All Amiodarone (*n* = 66) | All Procainamide (*n* = 31) |
|---|---|---|---|---|
| 62.2 (16) | 59.0 (19) | 80 | 65.1 (16) | 60.6 (18) |
| 5 (56) | 14 (67) | 0 (0) | 46 (70) | 19 (61) |
| 9.6 (3.8) | 6.2 (3.6) | 5 | 12.5 (2.4) | 7.2 (3.9) |
| 4 (44) | 14 (67) | 1 (100) | 43 (65) | 19 (61) |
| 0 (0) | 4 (19) | 0 (0) | 21 (32) | 4 (13) |
| 42.5 (14) | 37.9 (17) (*n* = 20) | 35 | 35.9 (15) (*n* = 65) | 39.2 (16) (*n* = 30) |
| 3 (33) | 9/20 (45) | 1 (100) | 35/65 (58) | 13/30 (43) |
| 4 (44) | 11 (52) | 0 (0) | 35 (53) | 15 (48) |
| 3 (33) | 6 (29) | 0 (0) | 21 (32) | 9 (29) |
| 3 (33) | 9 (43) | 0 (0) | 35 (53) | 12 (39) |
| 3 (33) | 8 (38) | 0 (0) | 22 (33) | 11 (35) |
| 1 (11) | 6 (29) | 0 (0) | 28 (42) | 7 (23) |
| 1 (11) | 2 (10) | 0 (0) | 15 (23) | 3 (10) |
| 3 (33) | 2/19 (11) | 0 (0) | 19/64 (30) | 5/29 (17) |
| 2 (22) | 7/20 (35) | 0/0 (0) | 13/63 (21) | 9/29 (31) |
| 160 (21) | 159 (27) (*n* = 20) | 187 | 167 (34) (*n* = 64) | 161 (25) (*n* = 30) |
| 147 (31) | 123 (27) (*n* = 20) | 70 | 115 (24) (*n* = 63) | 129 (31) (*n* = 30) |
| 76 (22) | 78 (15) | 0% (0/0) | 82 (18) | 77 (17) (*n* = 30) |
| 1 (11) | 4 (19) | 0 (0) | 10 (15) | 5 (16) |
| 1 (11) | 1 (5) | 0 (0) | 5 (8) | 2 (6) |
| 4.0 (0.5) | 4.0 (0.6) | 4.1 | 4.1 (0.6) (*n* = 64) | 4.0 (0.6) |
| 1.8 (0.2) | 1.8 (0.3) (*n* = 19) | 2 | 1.9 (0.3) (*n* = 58) | 1.8 (0.2) (*n* = 29) |
| 8.8 (0.6) | 9.2 (0.4) | 9.3 | 9.2 (0.7) (*n* = 63) | 9.1 (0.5) |
| 733 (384) | 900 (247) | 800 | 166 (47) | 848 (293) |
| 10.3 (5.5) | 11.8 (4.0) | (*n* = 0) | 2.1 (0.8) | 11.3 (4.5) (*n* = 30) |
| 19 (3) (*n* = 7) | 23 (10) (*n* = 17) | 13 | 15 (7) (*n* = 35) | 21 (9) (*n* = 25) |
| 1 (11) | 1 (5) | 0 (0) | 6 (9) | 2 (6) |
| 1.8 (0.8) | 2.1 (0.8) | 1.0 | 1.4 (0.6) | 2.0 (0.8) |
| 4 (44) | 3 (14) | 1 (100) | 42 (64) | 8 (26) |
| 0 (0) | 1 (5) | 0 (0) | 8/64 (13) | 1 (3) |
| 0 (0) | 13 (62) | 0 (0) | 35 (53) | 13 (42) |
| 1 (11) | 2 (10) | 1 (100) | 4 (6) | 4 (13) |
| 0 (0) | 0 (0) | 0 (0) | 1 (2) | 0 (0) |

administered over more than 20 minutes, the full dose of the bolus administered was recorded.

The predetermined time interval for successful termination was defined as 20 minutes because it was felt that clinicians would often not wait longer before initiating another treatment if the VT persisted. Because this could bias the outcome against successful procainamide treatment because procainamide often requires up to 1 hour for full loading as administered in our hospitals, a secondary effectiveness endpoint of the number of patients ultimately requiring electrical therapy such as DCCV was also measured.

Medication safety was a critical secondary outcome. The following were defined as clinically important adverse effects: change in systolic blood pressure (sBP) from greater than 90 mm Hg to less than 90 mm Hg, decrease in heart rate to less than 50 beats/min, any new dysrhythmia such as torsades de pointes, or any change in patient status requiring a new intervention such as IV fluid infusion or DCCV or requiring cessation of the study medicine infusion. All clinically important adverse effects occurring within 1 hour of initiation of study medicine infusion, and whether the effect led to cessation of the study drug infusion, were recorded. All sBP measurements within 1 hour of onset of study medicine infusion or until VT was terminated were recorded.

### Data Analysis

Reliability of the following major data points was assessed between the unblinded and blinded abstractors using unweighted Cohen's kappa: dose of study medicine infused, successful VT termination within 20 minutes of study medicine initiation, whether the patient was ultimately treated with electrical therapy, and clinically important adverse effects. Computations were performed with SPSS 15 (SPSS, Chicago, IL). Discrepancies were resolved by review of the medical record and consensus.

The primary and secondary effectiveness outcomes were determined for each of the two study drugs using exact statistics with Statxact 3 (Cytel Software, Cambridge, MA) to compute the proportions. The mean and median times to VT termination were computed with SPSS 15. Another secondary effectiveness outcome included an assessment of factors that may be associated with successful termination. Univariate associations were tabulated (Table 3).

Assuming VT termination rates of 30% and 70% for amiodarone and procainamide, respectively, equal group size, and an alpha of 0.05 and beta 0.20, a power calculation of an unadjusted univariate comparison indicated a necessary sample size of 24 patients in each group to determine the primary outcome.[5,6] The termination proportion for amiodarone was estimated based on the pharmacokinetics of relatively slow onset of refractory period prolongation and thus similar effectiveness to lidocaine.[6,9,10,16,17] The power to detect a difference in the two treatment groups could be increased or decreased in a multivariate analysis based on the additional explanatory information and degree of colinearity of the additional predictor variables included.

A planned multivariate logistic regression model using SPSS 15 was made and included the following independent variables potentially predictive of successful termination: patient history of MI, LVEF, the study medicine, dose per weight, and the interaction of the study medicine with dose per weight, because the two medicines are dosed differently.[15] A second multivariate model was made to adjust for unanticipated potentially confounding study characteristics, including order of treatment and recurrent VT despite ICD therapy before or during treatment. Study medicine and LVEF were retained from the original model. These two predictors were retained because the study medicine coefficient was of primary interest, and LVEF could be predictive based on the original model. Clinically important adverse effects were tabulated and the proportion of patients requiring cessation of study medicine infusion or immediate DCCV was determined for each medicine.

To determine the blood pressure response to medicine infusion during VT, a random effects mixed linear analysis was performed for each medicine using SAS 9 (SAS Institute, Cary, NC). Repeated measurements at various times represented a cluster of data for each patient, and the patients represented a random sampling from a population of VT patients. A mixed linear multivariate approach was used to model the dependent variable, sBP, as a function of the following potentially predictive fixed variables: time after initiation of infusion measured in minutes, the most recent sBP and heart rate prior to or at the time of study drug infusion, LVEF, order of treatment, recurrent VT despite ICD therapy before or during treatment, study medicine infused, and the interaction of these final six predictor variables with time. Random effect variables included in the model were an intercept and time after initiation of infusion (slope). The model contained a total of 13 fixed and two random effects. sBP was used because clinicians were often unable to measure the diastolic blood pressure.

## RESULTS

Four hospitals were included with a total enrollment of 97 study medicine infusions in 90 patients with VT (Table 1). Seven patients received both study medicines, including five during the same VT episode and two during different episodes of VT. The search methods included intentional overlap such that a patient with VT treated with a study medicine would be identified by both the diagnosis and the medication code. There was no evidence of patients who received a study medication but were not billed for it, and thus we are confident that all eligible patients were identified. The methods of proof of VT are listed in Table 2. Patient information including demographics, selected medical history, history of present illness, physical exam findings, electrolytes, treatment details, and associated MI are listed in Table 3 for patients who did and did not respond to amiodarone and procainamide. Patients who received another treatment within 20 minutes of initiation of study medicine infusion are listed as ''unknown'' outcome.

The fourth blinded data abstractor reviewed 55 charts, and kappa values for reliability of data abstraction were as follows: dose of medicine administered 0.97 (95% confidence interval [CI] = 0.90 to 0.99), VT termination within 20 minutes of study drug infusion 0.70 (95% CI = 0.52 to 0.88), final treatment electrical 0.89 (95% CI 0.77 to 0.99), and significant adverse effects 0.61 (95% CI = 0.34 to 0.89).

The response to treatment was known in 83 of 97 study medicine infusions in 76 patients. The proportion of patients with VT termination within 20 minutes of initiation of amiodarone infusion was 13/53 (25%, 95% CI = 14% to 38%), and for procainamide it was 9/30 (30%, 95% CI = 15% to 49%; Figure 1). The unadjusted

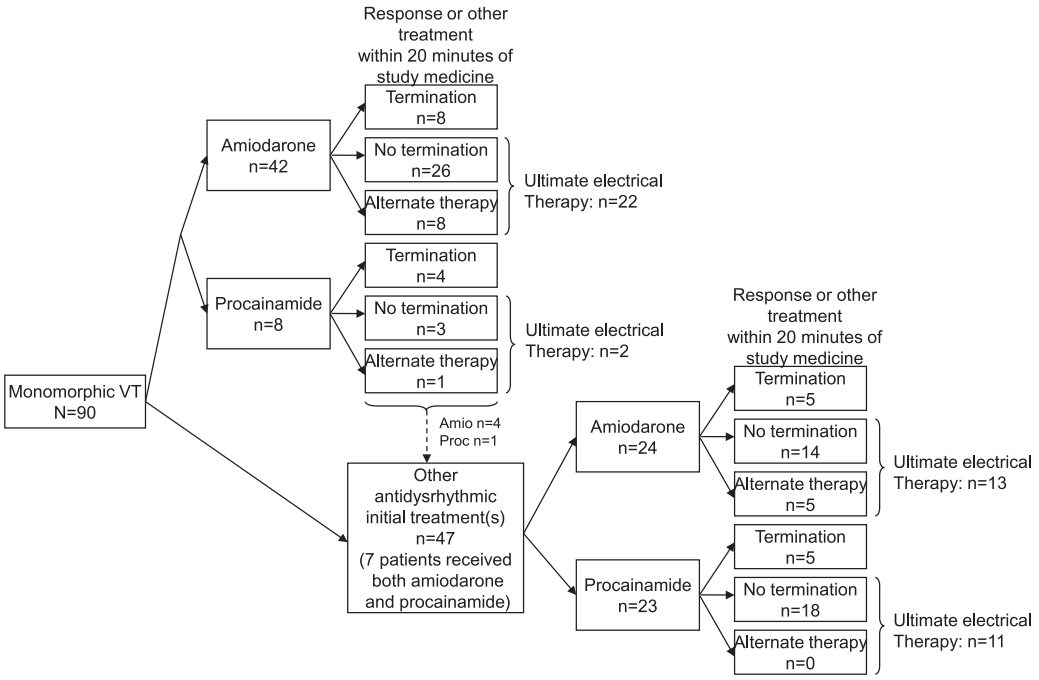


**Figure 1.** Patient flow algorithm. VT = ventricular tachycardia.

odds ratio (OR) for VT termination with procainamide compared to with amiodarone was 1.2 (95% CI = 0.5 to 3.6). For those patients who experienced VT termination within 20 minutes of onset of study medicine infusion, the mean time to termination was 11 minutes for both amiodarone and procainamide, and the median times were 10 and 13 minutes, respectively. For those patients with ''slow'' VT, with heart rate less than 150 beats/min, the proportions with VT termination were 4/20 (20%) and 2/9 (22%) for amiodarone and procainamide, respectively.

Another antidysrhythmic was administered prior to the study medicine in 47/97 (48%) episodes. Of these 47 episodes, the initial antidysrhythmic was lidocaine in 39 cases (83%). Eight of 47 (17%) received a second, and one of 47 (2%) received a third agent prior to the study medicine. Five patients received both study medicines during the same VT episode. Four patients received amiodarone first, and three of these four experienced VT termination after procainamide. One patient received procainamide first and subsequently experienced VT termination after amiodarone. Two patients received each study medicine during different VT episodes, and none of these four medicine administrations were associated with VT termination.

For those patients where amiodarone and procainamide were the initial antidysrhythmic treatments, the termination proportions were 8/34 (24%, 95% CI = 11% to 41%) and 4/7 (57%, 95% CI = 18% to 90%), respectively. Ultimately, 35/66 (53%, 95% CI = 40% to 65%) and 13/31 (42%, 95% CI = 25% to 61%) of amiodarone and procainamide patients required electrical therapy for termination of VT, respectively.

Comparisons of the proportions of patients with the primary outcome were performed using multiple logistic regression modeling. The response to treatment was known in 83 episodes, and one patient was missing data and was removed from both logistic regression models, leaving 82 episodes. None of the entered variables potentially predictive of VT termination were

Table 4
Adverse Effects Associated with Study Medicine Administration

| Adverse Effect | Amiodarone, *n* (%) | Procainamide, *n* (%) |
|---|---|---|
| Decrease in sBP from >90 mm Hg to <90 mm Hg | 7 (10.6) | 2 (6.5) |
| Decreased blood pressure requiring cessation of infusion | | 3 (9.7) |
| Decreased blood pressure requiring immediate direct current cardioversion | 4 (6.1) | 2 (6.5) |
| Decreased blood pressure in association with lopressor 2.5 mg IV requiring cessation of infusion | | 1 (3.2) |
| Asystole in association with lidocaine 200 mg IV infused 30 minutes prior to amiodarone | 1 (1.5) | |
| None | 54 (81.8) | 23 (74.2) |

IV = intravenous; sBP = systolic blood pressure.

statistically significant at the 0.05 level in the planned multivariate logistic regression model. LVEF had the strongest statistical association with a coefficient of 0.038 and the coefficient raised to the e power, EXP(LVEF) = $e^{0.038}$ = 1.04 (95% CI = 1.00 to 1.09). Thus, an absolute increase in LVEF of 10% would increase the odds of termination by an estimated factor of $e^{(0.038)(10)}$ = 1.5.

In the post hoc model, the only significant predictor of VT termination was EF with EXP(EF) = 1.03 (95% CI = 1.00 to 1.07). Based on the likelihood ratio test, the post hoc model, but not the planned model, had a significantly better fit (p = 0.01) than a univariate model with the treatment predictor only. The Hosmer-Lemeshow goodness-of-fit p-value for the post hoc model was 0.90 (p < 0.05 would suggest poor fit). The adjusted ORs of termination for the treatment variable, procainamide compared to amiodarone, in the planned and post hoc models were EXP(Rx) = 1.53 (95% CI = 0.84 to 2.76) and 1.21 (95% CI = 0.37 to 3.90), respectively.

Adverse effects associated with the study medicines are listed in Table 4. Hypotension led to cessation of medicine infusion or immediate DCCV in 4/66 (6%, 95% CI = 2% to 15%) and 6/31 (19%, 95% CI = 7% to 37%) patients who received amiodarone and procainamide, respectively. There were 261 total sBP measurements and 22 (8%) were removed from the mixed linear random effects regression model due to missing data in another included parameter. The model revealed that initial sBP (parameter estimate 0.92 [95% CI = 0.85 to 0.98]) and the interaction of initial sBP with time (parameter estimate −0.010 [95% CI = −0.019 to −0.0002]) were significantly predictive of sBP. Time, initial pulse, LVEF, order of treatment, recurrent VT despite ICD therapy before or during treatment, study medicine infused, and the interaction of each of these final five variables with time were not significantly predictive of sBP. For the interaction of study medicine infused and time predictor, where the study medicine dummy variable was given a value of 1 for amiodarone and 0 for procainamide, and time was measured in minutes, the adjusted parameter was 0.26 (95% CI = −0.30 to 0.81).

One patient, a 74-year-old man with a history of an ischemic cardiomyopathy and nonsustained VT with prior ICD implantation, died. He presented with recurrent VT despite repeated ICD shocks and 150-mg amiodarone bolus followed by 900 mg infused over 15 hours. His rhythm deteriorated to asystole without recovery 1 day after hospital admission.

## DISCUSSION

Procainamide was not found to be more effective than amiodarone for the acute termination of sustained VT in this study. However, our ability to compare the effectiveness of the two treatments was severely limited by the retrospective design of the study, a limited data set, and the potential for measured or unmeasured confounders. For these reasons, a direct comparison of effectiveness was only performed for the primary outcome using multiple logistic regression. Only those predictors thought clinically likely to confound the outcome were included to avoid overfitting the two models, and a second model was made to include confounders that were unanticipated when the study was designed in 2001. The treatment group effect estimate remained stable through both models, and the second model demonstrated good fit characteristics. Nevertheless, the possibility of unmeasured and unadjusted for confounders remains. For this reason, no firm conclusion can be drawn as to the relative effectiveness of the two medicines.

As currently used, neither amiodarone nor procainamide was highly effective. Procainamide may be more effective when used as an initial antidysrhythmic agent, but the termination rate of 57% (4/7) is based on too small a sample to draw conclusions.

It is possible that procainamide was less effective in this as compared to prior studies because the mean rate of infusion in this study was 21 mg/min compared to 50–100 mg/min in prior studies.[5,6,12] The Advanced Cardiac Life Support (ACLS) guidelines recommend an infusion rate of 20 mg/min to avoid hypotension.[1] However, the mean procainamide infusion rates in patients who did and did not experience VT termination in this study were 19 and 23 mg/min, respectively.

Procainamide may also have been less effective in this study because it was often not the first antidysrhythmic agent given. It may have been given preferentially to more refractory cases, or the previous medicines administered may have interfered with its actions. However, lidocaine, the agent most commonly administered prior to the study medicine, is not known to interact with either procainamide or amiodarone.[6,18–21] Finally, practicing physicians in this study may have been less tolerant of hypotension and stopped the procainamide infusion or electrically cardioverted the patient more often compared to investigators in prior prospective studies.

Decreased blood pressure is a concern for all patients receiving medical therapy for sustained VT. In this study, sBP trended down particularly for patients with a higher initial sBP. There was an adjusted trend of 2.6 mm Hg higher sBP for every 10 minutes after initiation of infusion in amiodarone compared to procainamide patients, but this difference was not statistically significant. Despite the inclusion of multiple potential confounders and a larger sample of interval sBP measurements to increase power, the estimate from this direct comparison may also be biased by unknown confounders. Procainamide infusion may have been stopped more often simply due to its generally longer duration compared to amiodarone. Not all patients receiving procainamide sustained a drop in sBP. Initial sBP, but not LVEF or initial heart rate, was predictive of a sBP drop.

In this study, where procainamide was most commonly administered according to the recommended ACLS protocol, its effectiveness for termination of VT was disappointing. Thirteen of 31 (42%) patients ultimately required electrical therapy. While procainamide seemed more effective when used as the initial agent (4/7, 57%), the numbers are too small to allow for meaningful comparisons. A trial of procainamide as the initial agent for VT termination administered at the ACLS recommended 20 mg/min infusion rate with an observation period up to 1 hour would be interesting.

However, such a trial might pose serious operational and safety concerns.

It may not be realistic to expect physicians in a busy emergency or cardiac intensive care setting to monitor a patient in VT for a prolonged period up to 1 hour while a potentially hypotensive agent such as procainamide is being infused. In this sample, 19% (6/31) of patients treated with procainamide required cessation of infusion or immediate electrical cardioversion for hypotension. Of the eight patients who received procainamide as the initial agent (one with unknown outcome), two suffered decreased blood pressure and one of these two required cessation of the infusion. Prior reported rates of hypotension or destabilization with more aggressive dosing regimens include 0% (0/15), 13% (2/15), and 20% (2/10).[5,6,12] It may be difficult to justify even the experimental use of a medicine with an unpredictable propensity for hypotension when a safe and effective alternative modality, synchronized DCCV, exists.

At present, no medication seems both highly effective and safe as initial therapy for termination of sustained VT. Synchronized DCCV, under conscious sedation if possible, is safest and most effective.[22] However, medications play an important role for patients with recurrent sustained VT despite electrical therapy. The optimal medical regimen in this situation remains unknown.

## LIMITATIONS

The major limitations of this study are primarily a result of its retrospective nature and the limited use of procainamide by practicing physicians in the study hospitals. There was potential for bias in the choice of medicine used by the clinicians and their assessment of its efficacy and adverse effects. The study spanned 15 years of practice and the mean year of study enrollment was 7.2 for procainamide and 12.5 for amiodarone. Procainamide was used less often in the later years and IV amiodarone was not widely available before approximately 2000. The incidence of illness has likely changed, with more patients today receiving aggressive treatment for acute MI and fewer suffering from large scars with localized altered conduction and subsequent VT. Chronic treatment has also changed, most notably with the widespread use of ICD implantation. The prevalence of an ICD was almost twice as great in the amiodarone sample of this study. ICDs did not always deliver therapy, however, and the most common reason for this was because the rate of VT was below the therapeutic rate threshold set for the ICD.

The study medicine was often not the first medicine used to treat VT, and amiodarone was more commonly used earlier in relation to other medicines. For this reason, separate reporting was provided of only those cases where the study medicine was used first. It is important to note, however, that lidocaine was the agent used most commonly prior to the study medicine, and when administered alone, it is unlikely to terminate sustained VT that is not associated with an acute MI or to cause hypotension.[6,16,17]

The interval allowed for successful VT termination was 20 minutes after the onset of study drug infusion. This may bias against procainamide, which is often infused over 1 hour. However, physicians often initiated another treatment between 20 and 60 minutes after initiation of the study medicine infusion, so the response would be confounded if the duration of observation was extended. Reporting of the proportion of patients ultimately requiring electrical therapy was provided to assess study medicine performance independent of a defined observation period.

There may have been bias in investigator recording and analysis of data. A protocol with detailed methodology was written prior to initiation of the study to minimize this. Results of the reliability analysis with a blinded investigator were reassuring. Incomplete data was a potential problem, but the primary outcome of VT termination was generally explicitly noted in the chart because it was the focus of care. Blood pressures were recorded at unstandardized times, and this was addressed with the mixed linear random effects analysis.

## CONCLUSIONS

Procainamide was not significantly more effective than amiodarone for the termination of spontaneous sustained ventricular tachycardia; however, the confidence of this comparison was highly limited by the study design and possible unmeasured confounders. Termination rates were low for both medicines. In 19% (6/31) of patients who received procainamide infusion, treatment had to be altered due to hypotension. However, procainamide was not associated with a significantly greater drop in systolic blood pressure than amiodarone after adjusting for initial systolic blood pressure values. Left ventricular ejection fraction was not associated with a change in systolic blood pressure. Initial medical therapy may be preferred for some patients with sustained ventricular tachycardia, but as currently administered, neither procainamide nor amiodarone can be routinely recommended as primary therapy over synchronized direct current cardioversion.

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