Incidence of Cardiac Arrhythmias During Intravenous Pentamidine Therapy in HIV-Infected Patients*

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Study objective: There have been 15 published cases of probable pentamidine-induced torsade de pointes (Tdp). A prospective analysis of this complication of therapy is valuable considering the high frequency of Pneumocystis carinii pneumonia in the AIDS population, and the role of pentamidine in its therapy.

Design: Open, nonrandomized, prospective study of HIV-infected patients receiving intravenous pentamidine in a 12-month period.

Setting: Walter Reed Army Medical Center, a tertiary care, referral-based facility in Washington, DC.

Patients: Eighteen HIV-infected patients were enrolled with informed consent; four were withdrawn from statistical analysis after receiving only one or two doses of empiric intravenously administered pentamidine.

Measurements and results: Daily 12-lead electrocardiography, echocardiography, weekly signal-averaged electrocardiography, and weekly 24-h ambulatory electrocardiography were performed on each patient. Of the 14 subjects, 3 developed Tdp. These 3 patients and 2 others developed a prolonged rate corrected, QT interval (QTc) to greater than 0.48 s (max QTc mean, 0.55 s, mean increase, 0.12 s). The QTc prolongation was noted in all five patients by the fourth daily dose (4 mg/kg) of pentamidine. The other 9 patients developed minimal change in QTc intervals throughout therapy (max QTc mean, 0.45 s; mean increase, 0.03 s). The maximum QTc increase was significantly different between these two cohorts (p < 0.03). The occurrence of Tdp in the subgroup of patients developing prolonged QTc intervals to greater than 0.48 s (3 of 5 patients), or a change in QTc of greater than 0.08 s (3 of 4 patients) over individual baseline also was significant (p = 0.03 and p = 0.01, respectively). No baseline clinical variables associated with Tdp or QTc prolongation were identified.

Conclusion: Intravenously administered pentamidine frequently results in QTc prolongation with a subsequent risk of Tdp in HIV-infected patients. All patients treated with intravenously administered pentamidine should be evaluated with baseline and daily ECGs, at least during the first week of therapy, and should be closely monitored for a change in the QT interval. An increase in QTc to above 0.48 s or greater than 0.08 s above baseline carries a significant risk for proarhythmia and, in this instance, continuous electrocardiographic monitoring or an alternative antibiotic regimen should be considered.

(Chest 1994; 105: 389-94)

More than 60 percent of patients with AIDS develop Pneumocystis carinii pneumonia (PCP). While the trimethoprim sulfamethoxazole (TMP-SMX) combination is considered as first-line therapy, its use is limited by adverse reactions in many AIDS patients. When TMP-SMX fails or is contraindicated, intravenously administered pentamidine isethionate usually is the next antimicrobial agent chosen. However, therapy with pentamidine also may be limited by toxicities including transaminitis, creatinine elevation, dysglycemia, hypotension, anemia or neutropenia, and pancreatitis.

To date, there have been 15 published case reports of probable pentamidine-induced torsades de pointes (Tdp). Despite these reports, a precise cause-and-effect relationship between pentamidine and Tdp has remained debatable since most of these cases occurred during the administration of other medications or in the setting of significant electrolyte abnormalities, both of which can be associated with Tdp.

Given the high frequency of PCP in the AIDS population, and the significant role of pentamidine in its therapy, we felt that a prospective analysis of this complication of therapy was warranted. Furthermore, the identification of possible predictors of this complication is clinically useful.

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PCP = Pneumocystis carinii pneumonia; QTc = rate-corrected QT interval; SAECG = signal-averaged electrocardiogram; Tdp = torsades de pointes; TMP-SMX = trimethoprim sulfamethoxazole

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PATIENTS AND METHODS

Clinical Data

During a 12-month study period, all patients receiving pentamidine intravenously at Walter Reed Army Medical Center, Washington, DC, were identified by the hospital pharmacy. Each was verified to be eligible for inclusion, and was enrolled with informed consent according to the guidelines of this institution's Department of Clinical Investigation. Exclusion criteria included a previous history of cardiac disease or arrhythmia; electrolyte abnormalities; concomitant use of other drugs associated with arrhythmias (specifically TdP), including type IA and type III antiarrhythmic drugs, tricyclic antidepressants and phenothiazines; ischemia on a baseline ECG; prolonged rate corrected QT interval (QTc) at baseline (> 0.48 s); and the presence of other conditions which have been associated with TdP (central nervous system disorders, congenital long QT interval syndrome, pacemaker use, liquid protein diets, significant bradycardia, organophosphate toxins).15,16

None of the patients identified was excluded by these criteria.

An index case and 17 consecutive patients were prospectively evaluated with baseline 12-lead electrocardiography, transthoracic two-dimensional and Doppler echocardiography, and 240-beat signal-averaged electrocardiography (SAECG). Thereafter, daily 12-lead ECGs were performed for the duration of pentamidine therapy, as well as weekly SAECG and 24-h ambulatory ECGs (Marquette Electronics, Inc., Jupiter, Fla). The SAECG, ambulatory monitors, and echocardiograms were blindly interpreted by a board-certified cardiologist. The daily ECGs were evaluated and the computer-derived interval measurements were confirmed and corrected where necessary. The QT interval was measured from the earliest deflection of the QRS segment to the return of repolarization to the TP segment. The QTc was calculated conventionally using Bazett's equation.17 Studies subjects were given pentamidine isethionate as intravenous infusions via peripheral catheter over 1 h (4 mg/kg/dose). Serum electrolytes, magnesium, calcium, creatinine, and glucose levels were measured at least four times per week as well as at the time of any arrhythmic event. Serum electrolyte abnormalities were corrected at the discretion of the patient's primary physicians.

Four of the 18 patients enrolled were withdrawn from statistical analysis because the diagnosis of PCP was not confirmed by bronchoscopy and they received less than 3 doses of empiric intravenously administered pentamidine. These excluded patients had baseline characteristics similar to the study group and had no documented arrhythmias or change in QTc. Patient characteristics for the remaining patients are displayed in Table 1. Six of these patients were reclassified as Walter Reed stage VI HIV disease with this episode of PCP; namely, this was their first opportunistic infection identified, or their AIDS-defining illness.18

Statistical Analysis

Comparisons between groups were conducted using Fisher's exact test (two-tailed), the Mann-Whitney (rank sum) test, or the two-sample Student's t test. A probability value of 0.05 or less was considered significant.

RESULTS

Five patients developed significantly prolonged QTc during intravenous pentamidine therapy with a mean increase of 0.12 ± 0.03 s over baseline, to a mean maximum QTc of 0.55 ± 0.02 s. The QTc prolongation was sustained in 4 of these 5 patients. The other 9 patients had minimal change in QTc intervals throughout therapy (mean increase of only 0.03 ± 0.02 s; mean maximum QTc, 0.45 ± 0.03 s).

Three patients, all of whom had significantly prolonged QTc intervals, developed electrocardiographically proven TdP. The arrhythmia was identified in two of the three patients at the bedside with 12-lead ECGs taken to evaluate nonspecific symptoms such as palpitations, nausea, dizziness, or rigor. The third patient was under continuous monitoring in the ICU, where he had previously been transferred for respiratory distress. Baseline QTc

Table 1—Patient Characteristics

<table>
<thead>
<tr>
<th>Patient</th>
<th>Age (yr), Race, Sex</th>
<th>HIV Positive, mo</th>
<th>No. Days Therapy</th>
<th>LVEDW/LVESW</th>
<th>LV Function</th>
<th>% Increase in QTc</th>
<th>Result</th>
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<tr>
<td>1*</td>
<td>34, B, M</td>
<td>23</td>
<td>8</td>
<td>49/36</td>
<td>Normal</td>
<td>+37</td>
<td>+ TdP</td>
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<tr>
<td>2*</td>
<td>43, B, F</td>
<td>54</td>
<td>10</td>
<td>50/35</td>
<td>Mild global</td>
<td>+24</td>
<td>+ TdP</td>
</tr>
<tr>
<td>3*</td>
<td>48, B, F</td>
<td>8</td>
<td>16</td>
<td>48/30</td>
<td>Hypokinesis</td>
<td>+30</td>
<td>+ TdP</td>
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<tr>
<td>4†</td>
<td>45, H, M</td>
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<td>11</td>
<td>45/28</td>
<td>Normal</td>
<td>+29</td>
<td>Increased QTc</td>
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<tr>
<td>5†</td>
<td>35, B, M</td>
<td>52</td>
<td>18</td>
<td>50/38</td>
<td>Normal</td>
<td>+16</td>
<td>Increased creatinine, end course</td>
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<tr>
<td>6</td>
<td>45, B, M</td>
<td>52</td>
<td>5</td>
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<td>n/a</td>
<td>+8</td>
<td>PCR not confirmed</td>
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<tr>
<td>7</td>
<td>35, W, M</td>
<td>46</td>
<td>9</td>
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<td>End course</td>
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<td>15</td>
<td>48/30</td>
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<td>11</td>
<td>67, B, M</td>
<td>29</td>
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<td>60/50</td>
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<td>72</td>
<td>10</td>
<td>52/30</td>
<td>Normal</td>
<td>+7</td>
<td>Change p.o. dapsone/TMP</td>
</tr>
</tbody>
</table>

*Patient developed QTc prolongation and TdP.
†Patient developed sustained prolonged QTc, using criteria in text, with no evidence of arrhythmia.
§Patient had abnormal QTc only once, associated with marked tachycardia.
§§Black = black; H = Hispanic; W = white.
||LVEDW = left ventricular end-diastolic width in millimeters (normal, 35 to 57 mm); LVESW = left ventricular end-systolic width in millimeters (normal, ≤40 mm).
|LV function = left ventricular systolic function as evaluated by two-dimensional echocardiography.
"n/a" = data not available.

Cardiac Arrhythmias During IV Pentamidine Therapy (Eisenhauer et al)
intervals between these two cohorts (TdP vs no TdP) was not different (p = 0.69, Fig 1, B), and was not useful in identifying patients at risk for developing TdP. Minimum K+ and Mg++ values measured during intravenous pentamidine therapy in these same two cohorts also were not statistically different (p = 0.58 and p = 0.31, respectively, two-sample Student's t test). Serum K+ and Mg++ were normal at the time of arrhythmic event in all three (K+ ≥ 3.6 and ≤ 5.2 mEq/L, Mg++ ≥ 1.7 and ≤ 2.9 mg/dl).

The occurrence of TdP or persistent QTc prolongation prompted prompt ICU monitoring and discontinuation of pentamidine therapy in four patients. The fifth patient had a single isolated QTc elevation after a cumulative dose of 8 mg/kg only, which was likely related to a weakness in Bazett's equation since his heart rate was more than 100 beats per minute on that ECG and in the low 80s both one day before and afterward. The mean maximum QTc value in those patients with TdP was significantly higher than in those patients who did not develop TdP (p < 0.03, Fig 1, B). TdP occurred in 3 of 5 patients with an increase in absolute QTc to greater than 0.48 s (p = 0.03), and in 3 of 4 patients with an increase in QTc greater than 0.08 s from baseline (p = 0.01; Table 2). The fourth patient with an elevated QTc did not develop TdP, but intravenous pentamidine therapy was discontinued because of persisting QTc prolongation. The time required for normalization of the QTc interval after pentamidine therapy was discontinued varied from 2 to 3.5 days (mean, 2.9 days).

Ultimately, two patients became hemodynamically unstable during recurrent TdP events and required emergency cardioversion. Two of the three patients developing TdP survived. Despite a change in therapy and appropriate management of TdP,16.19 patient 2 (Table 1)

![Figure 1A](image1.png)

**Figure 1A.** The QTc interval vs. cumulative dose pentamidine, in standard dose intervals (4 mg/kg/dose).

Numbers signify patient number. Stars represent torsades de pointes. B, QTc ranges, baseline and maximum, during therapy, comparing torsades de pointes vs no torsades de pointes groups. Brackets indicate ± SD from the mean. Asterisk indicates Mann-Whitney test.

![Figure 1B](image2.png)

**Figure 1B.**

| Table 2—Occurrence of Torsades de Pointes Using Alternative QTc Interval Criteria* |
|---------------------------------|--------|--------|--------|--------|
|                                | Max QTc >0.48 | Max QTc <0.48 | Rise in QTc >0.08 | Rise in QTc <0.08 |
| TdP                            | 3/5     | 0/9     | 3/4     | 0/10   |
| No TdP                         | 2/5     | 0/9     | 1/4     | 10/10  |
| Probability†                   | . . .   | 0.03    | . . .   | 0.01   |

*A higher risk of arrhythmia was observed in patients prolonging QTc interval to greater than 0.48 s, or increasing QTc more than 0.08 s over individual baseline (pre-pentamidine administration) QTc. †Fisher's exact test, two tailed.
continued to suffer from repeated episodes of hemodynamically significant 
TdP, required electrical cardioversion and transvenous pacing, and ultimately 
died from respiratory failure. Postmortem examination revealed no pathologic evidence of myocarditis, necrosis, or cellular infiltrates.
Patient 1 was successfully switched to inhaled aerosolized pentamidine and recovered. This patient died 18 months later from an apparent cardiopulmonary arrest in a nonmonitored setting; postmortem examination was not obtained. Therapy for patient 3 was changed to orally administered dapsone and TMP and the patient is presently alive and well, with no evidence of subsequent arrhythmias.

Figure 1A displays the absolute QTc vs cumulative dose. An early and rapid increase in QTc was discovered in those patients who developed significant prolongation and, in three cases, TdP. If the patient developed a significantly prolonged QTc during therapy, it occurred quickly, after only three or four doses of intravenously administered pentamidine.

The change in QTc also demonstrates these results dramatically (Fig 2A and B), showing that an increased QTc of between 0.08 and 0.10 s signals an increased risk of developing TdP (p < 0.02). The patient (No. 2) who ultimately developed TdP at a point when the QTc was increased less than 0.08 s actually satisfied this criterion earlier in the treatment course.

Left ventricular chamber sizes, as measured by end-diastolic and end-systolic widths, were normal in all five subjects who developed prolonged QTc interval (Table 1).26 One of the subjects who developed TdP was noted to have a mild global hypokinesis of the left ventricle. The only subject to have an abnormally large left ventricular chamber size with coexisting decreased function did not develop a detectable arrhythmia.

All SAECG recordings were within the range of normal using standard criteria to evaluate late ventricular potentials and showed no change during pentamidine administration.21-23

Ambulatory electrocardiographic monitoring was useful only in retrospect, providing full disclosure of cardiac rhythm before and after episodes of arrhythmia. Findings included ventricular bigeminy, T-wave alternans, and long cycle-short cycle sequences of pre-

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**Figure 2A.** Change in QTc interval vs cumulative dose pentamidine, in standard dose intervals (4 mg/kg/dose). Shaded area represents the change in QTc level above which the development of torsades de pointes is more likely, warranting an increased vigilance to include continuous electrocardiographic monitoring. Numbers signify patient number. Stars indicate torsades de pointes. B, Change in QTc interval, torsades de pointes vs no torsade de pointes. Brackets indicate ± SD from the mean. Asterisk indicates Mann-Whitney test.

**Figure 2B.**
mature ventricular complexes, all of which have been commonly described in drug-induced TdP.

**DISCUSSION**

Torsades de pointes is distinguished from other forms of polymorphic ventricular tachycardia by its characteristic morphologic features and by its occurrence in association with a prolonged QT interval. Pentamidine is believed to cause both QT interval prolongation and TdP, which has been documented in case reports. However, a number of these reports were incomplete and many were confounded by coexistent electrolyte abnormalities.

Prior experience with pentamidine may not have identified TdP as a significant adverse event because ECGs and cardiac monitoring have not been routinely performed. Some patients with TdP are relatively asymptomatic, and this arrhythmia may not be recognized unless the physician suspects this potential hazard. Our study adds new information to the previously reported cases and highlights the significant incidence of cardiac arrhythmias during intravenous pentamidine therapy in HIV-infected patients, particularly with concomitant normal electrolyte levels.

Two other prospective studies have evaluated electrocardiographic consequences of pentamidine administration. In a study using standard 12-lead electrocardiography every 3 days, Stein et al. observed QTc prolongation and a high frequency of coexisting hypokalemia in 10 of 32 patients treated with intravenously administered pentamidine. Although the incidence of arrhythmias was not specifically addressed, the authors reported frequent or complex ventricular ectopy in two of the patients with QTc prolongation but no sustained or symptomatic arrhythmias. In a letter, Gonzalez et al. also reported on the utility of repeat ECG after 7 days of pentamidine administration. Of ten patients, one developed QTc prolongation and no arrhythmias were documented. Taking together our own data with the previously mentioned reports, the incidence of QTc prolongation during intravenous pentamidine administration is 27 percent (15 of 56). In the setting of QTc prolongation, the risk of developing potentially life-threatening arrhythmias is higher, with a 60 to 75 percent incidence in our study, dependent upon which criterion (QTc > 0.48 s, or increase in QTc > 0.08 s) is used.

We found no baseline characteristics which predicted the subsequent development of QTc prolongation or TdP, including baseline QTc, abnormal SAECG, or echocardiographic evidence of structural heart disease. However, an increased risk of developing TdP during pentamidine administration may be best identified through frequent monitoring of the QTc interval. As commonly seen with other drugs that induce TdP, such as quinidine, in our study an increase in QTc was most common during the first few days of pentamidine administration. Because of this, pentamidine-associated QTc prolongation and TdP appear to be idiosyncratic phenomena, rather than cumulative dose-related effects. This is evidenced by both the rapid and early increase in QTc interval in those patients developing QTc prolongation, and the absence of a continued progressive increase in QTc despite extended administration of pentamidine in the majority of study subjects. This hypothesis contrasts with both the current case report-based literature, as well as with other previously evaluated noncardiac toxicities of pentamidine; noncardiac toxicities have been shown to correlate more closely with cumulative parenteral dose rather than measured blood levels, since the drug is thought to be largely tissue-bound.

Possible mechanisms that have been suggested to explain pentamidine-induced arrhythmias include the induction of intracellular as well as extracellular electrolyte abnormalities, and a mimicry of the electrophysiologic effects of procainamide based upon structural similarity between these drugs. Ventricular ectopy and arrhythmias also are within the spectrum of cardiac abnormalities described in HIV infection. However, the occurrence of polymorphic ventricular tachycardias in the setting of QTc interval prolongation is much more consistent with an induced drug effect rather than from myocarditis or HIV cardiomyopathy. The significance and extent of cardiac disease in the HIV-infected population is a subject of ongoing study. Presently, limited data are available describing clinical cardiac abnormalities in patients with AIDS or in HIV-infected patients who have not demonstrated an opportunistic infection.

**LIMITATIONS**

Although we did not observe any arrhythmias in the group without QTc prolongation, continuous telemetric monitoring was not available. The possibility of silent, undocumented arrhythmias in these patients cannot be definitively excluded because drug-induced polymorphic ventricular tachycardia has been described in patients with normal or mildly increased QT intervals. Serum pentamidine levels were not performed; however, the utility of such levels is limited due to extensive tissue deposition. Certainly, HIV-infected patients with Pneumocystis pneumonia are frequently very ill and are given multiple drug regimens. Corticosteroids, which are frequently administered to patients with Pneumocystis pneumonia, can result in electrolyte abnormalities and thereby may increase the potential for proarrhythmia in patients receiving pentamidine. Although serum electrolyte levels were normal in all patients at the time of TdP, these may not be reflective of intracellular concentrations. Ketoconazole, an oral antifungal agent commonly prescribed to HIV-infected patients to control oral candidiasis, is known to be a potent inhibitor of metabolism of a variety of drugs via nonspecific inhibition of
cytochrome P-450 enzymes. It is possible that ketoconazole may inhibit the metabolism of pentamidine, in a manner similar to that recently demonstrated by terfenadine-ketoconazole interaction, although such an interaction remains to be proven. Both ketoconazole (patients 2, 3, 7, and 12) and a similar azole agent, fluconazole (patients 5, 6, 8, 10, and 11), were concomitantly administered during this study. Our study population was limited in size not only because of the 12-month enrollment period, but also because of a perceived institutional fear of pentamidine-induced cardiac arrhythmias based on our early experience. In addition, a new phase III multicenter trial comparing the efficacy of alternate drug regimens for PCP was initiated and absorbed a majority of patients infected with Pneumocystis.

**CLINICAL IMPLICATIONS**

Intravenous administration of pentamidine carries a high risk of QTc interval prolongation and subsequent torsades de pointes. We recommend that every patient to be treated with intravenously administered pentamidine be evaluated with a baseline and then daily ECG, at least for the first 5 to 7 days of therapy, and closely monitored for a change in the QTc. An increase in the QTc above 0.48 s or greater than 0.05 s above the baseline QTc indicates a significant potential risk for proarrhythmia. In this instance, pending further study we recommend continuous electrocardiographic monitoring or consideration of an alternative antibiotic regimen.

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