Incidence of drug-induced torsades de pointes with intravenous amiodarone

Jayaprakash Shenthar*, Jayasheela Mambally Rachaiah, Vivek Pillai, Siva Sankara Chakali, Vidhyakar Balasubramanian, Manjunath Chollenhalli Nanjappa

Sri Jayadeva Institute Of Cardiovascular Sciences and Research, 9th Block Jayanagar, Bannerghatta Road, Bengaluru 560069, India

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A B S T R A C T
Aim: To define the incidence, presentation, and outcomes of drug-induced Torsades de Pointes (TdP) with intravenous (IV) amiodarone.

Methods: From January 2014 to August 2016 a total of 268 patients received IV amiodarone, 142 for ventricular tachycardia, 104 for atrial flutter/fibrillation, and 22 for incessant atrial tachycardia. A uniform dosing of amiodarone to yield 1 gm/day was used in all patients.

Results: Four of the 268 patients (M:F 1:3) with mean age of 51.25 ± 9.17 years developed pause dependent TdP degenerating to VF, after a mean dose of 690 ± 176.63 mg, infused over 12 ± 5.88 h. The QTc that was 505 ± 9.02 ms at the time of TdP normalized to 433.75 ± 6.13 ms 48–72 h after stopping amiodarone. There was no immediate or late mortality, and patients are well at 5–10 months of follow-up. None of the patients tested positive for LQTS genes.

Conclusion: The incidence of drug-induced TdP with IV amiodarone is about 1.5%. Risk factors include female sex, left ventricular dysfunction, electrolyte abnormalities, baseline prolonged QTc, concomitant beta-blocker, and digoxin therapy. Amiodarone induced TdP has favorable prognosis if recognized and treated promptly, and these patients should not receive amiodarone by any route in future.

* Corresponding author at: Electrophysiology unit, Department of Cardiology, Sri Jayadeva Institute of Cardiovascular Sciences and Research, Bengaluru, India.
E-mail address: jshenthar@yahoo.com (J. Shenthar).

1. Introduction

Amiodarone a class III antiarrhythmic exhibits low frequency of pro-arrhythmic events despite causing QT prolongation.1 Intravenous (IV) amiodarone is useful for the treatment of recurrent, hemodynamically unstable VT/VF.2 It also effective for ventricular rate control in critically ill patients with atrial tachyarrhythmias and rapid ventricular response refractory to conventional atrioventricular blocking drugs.3 The recent European guideline suggests that in patients with atrial fibrillation who are critically ill or in patients who have severely impaired LV systolic function, where excess heart rate is leading to hemodynamic instability, intravenous amiodarone can be used for ventricular rate control.4 Amiodarone is presumed to have a low incidence of drug-induced torsades de pointes (TdP) with an incidence of <0.5%.1 In many parts of the world, amiodarone is the only intravenous antiarrhythmic drug available for acute treatment of arrhythmias, and it has been used extensively with the assumption of a low incidence of proarrhythmia. Contrary to this assumption, epidemiological and population-based studies indicate that amiodarone is the most common cause of drug-induced TdP. From these studies, it appears that about 50% of drug-induced TdP occurs in those who receive intravenous amiodarone and it is an under-recognized entity.5,6 The presumption of the low incidence of proarrhythmia appears to be based on studies of its chronic oral use and not by the intravenous route. The risk factors, recognition, the time course of occurrence, and outcomes for drug-induced TdP with IV amiodarone have not been well characterized. TdP is an uncommon but potentially fatal arrhythmia that can be caused by drugs. It’s time course of occurrence, recognition of risk factors, and management strategies may help to reduce mortality and morbidity.7 We report a case series of four patients who developed amiodarone-induced TdP degenerating to ventricular fibrillation with intravenous amiodarone therapy and discuss its recognition, time course of occurrence, possible mechanism, risk factors, management, and strategies to reduce the risk of drug-induced TdP.

Abbreviations: TdP, torsades de pointes; IV, intravenous; DC, direct current; CV, cardioversion; NYHA, New York Heart Association; AF, atrial fibrillation; VT, ventricular tachycardia; VF, ventricular fibrillation; LQT, long QT; LQTS, long QT syndrome; LVEF, left ventricular ejection fraction.

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ventricular tachycardia, were reviewed. The institutional protocol for infusion of IV amiodarone was uniform. Briefly, it involved dilution of 3 mL of amiodarone injection (150 mg) in 100 mL D5W (concentration of 1.5 mg/mL). The solution was infused over 10 min (15 mg/min) for a total of 150 mg and continued with a slow infusion of 900 mg of amiodarone in 500 mL D5W (1.8 mg/mL). The injection was administered at a rate of 1 mg/min for 6 h, providing 360 mg over that 6 h, and 510 mg (360 mg + 150 mg) over 6 h 10 min followed by a maintenance infusion at a rate of 0.5 mg/min, which over 18 h would total about 540 mg. This protocol would infuse approximately 1050 mg of amiodarone over the first 24 h. If the arrhythmia did not convert to sinus rhythm or the ventricular rate control was not achieved after 24 h of infusion, or any patient developed hemodynamic deterioration in the first 24 h they were subjected to DC cardioversion. For treatment after the first 24 h, the maintenance infusion of 0.5 mg/min, or 30 mg/h, was continued if necessary for further 48 h. Data of patients who developed TdP with intravenous amiodarone was analyzed.

The data collected included age, sex, symptoms, underlying cardiac disease, medications at the time of presentation, heart rate, blood pressure, baseline and serial ECG’s, electrolytes including serum potassium, calcium, and magnesium, renal function tests, 2D Echo-Doppler study. All the ECGs were recorded at 10 mV/mm and 25 mm/s speed. The QT interval was measured immediately after patients resumed sinus rhythm. QT interval was measured from the onset of the QRS interval to the end of the T-wave in all the leads where the end of the T-wave could be clearly defined. The longest QT interval in any of these leads was used as “QT.” This QT interval was then corrected for the heart rate with the preceding time duration between 2 consecutive R waves of the ECG (RR interval) and the Bazett formula (corrected QT [QTC] interval QT/square root of RR interval in seconds). The total dose of amiodarone was calculated based on the duration of infusion. Time to onset of TdP, treatment given, outcomes, and time to normalization of QT interval were analyzed. All four patients who developed drug-induced TdP underwent genetic analysis for the 13 most common genes of long QT syndrome (AKAP9, ANK2, CACNA1C, CAV3, KCNE1, KCNE2, KCNH2, KCNJ2, KCNJ5, KCNJQ1, SCN4B, SCN5A, SNTA1).

### Table 1
Baseline characteristics of the study population.

| Total Patients | N = 268 |
|----------------|---------|
| **Sex (M: F)** | 152(55.97%): 116(44.03%) |
| **Indication:** | | 
| VT | 142 (52.98%) |
| AF | 104 (38.81%) |
| AT | 22 (8.21%) |
| **Concomitant drugs:** | | 
| Beta blockers | 30 |
| Digoxin | 10 |
| Verapamil | 4 |
| **Heart rate during arrhythmia** | | 
| LVEF | 43 ± 23 bpm |
| **Ventricular tachycardia** | | 
| N = 142 | | 
| - Amiodarone started after DCCV | 24 (16.9%) |
| - Amiodarone used as first line therapy | 118 (83.1%) |
| - Successful reversion with Amiodarone alone | 64/118 (54.24%) |
| - Failed reversion needing DCCV | 38/118 (32.20%) |
| - Hemodynamic instability needing DCCV | 16/118 (13.56%) |
| **Atrial fibrillation/flutter** | | 
| N = 104 | | 
| - Successful reversion with Amiodarone alone | 40 (38.46%) |
| - Failed reversion needing DCCV | 36 (34.62%) |
| - Hemodynamic instability needing DCCV | 6 (5.77%) |
| - Rate control alone achieved | 22 (21.15%) |
| **Atrial tachycardia** | | 
| N = 22 | | 
| - Successful reversion with Amiodarone alone | 2 (9.09%) |
| - Successful DCCV | 2 (9.09%) |
| - Unsuccessful DCCV | 18 (81.81%) |

### Table 2
Characteristics of patients who had Amiodarone Induced TdP.

| Age (years) | Case 1 | Case 2 | Case 3 | Case 4 |
|-------------|--------|--------|--------|--------|
| Gender | Female | Female | Male | Female |
| Symptoms | Dyspnea 20 days | Dyspnea, Palpitations 2 days | Dyspnea 4 days | Dyspnea, Palpitations 3 days |
| Rhythm | Atrial Flutter | Atrial Fibrillation | Ventricular Tachycardia, Cardioverted | Atrial Fibrillation |
| Ventricular rate | 150 bpm | 143 bpm | 146 bpm | 143 bpm |
| Underlying heart disease | RHD: Tight MS | Tachy-Brady with VVI Pacemaker, HTN | Dilated Cardiomyopathy | Hypertension, Diabetes, Normal CAG |
| LVEF | 55% | 53% | 32% | 48% |
| Medications | Atenolol 25 mg/d | Bisoprolol 5 mg/d | Atenolol 50 mg/d | Atenolol 10 mg/d |
| Dose of Amiodarone | 510 mg | 630 mg | 930 mg | 690 mg |
| Duration of infusion | 6 h | 10 h | 20 h | 12 h |
| Underlying rhythm at the time of TdP | AF with slow VR | Pharmacological CV to sinus rhythm | Sinus rhythm | Pharmacological CV to sinus rhythm |
| Heart rate at the time of TdP | 53 bpm | 56 bpm | 53 bpm | 50 bpm |
| QTc at the time of TdP | 500 ms | 512 ms | 497 ms | 506 |
| QTc on follow up | 437 ms | 440 ms | 454 ms | 432 |
| Isoprenaline | Yes | Yes | Yes | Yes |
| Magnesium | Yes | Yes | Yes | Yes |
| Lignocaine | Yes | Yes | Yes | Yes |
| Pacing | No | Yes | Yes | No |
| Follow up | 10 months | 7 mths | 6 mths | 5 months |

* Permanent pacemaker programmed to 90 bpm for 48 h.

b Developed ventricular flutter 5 min after starting Isoprenaline. After defibrillation, temporary pacemaker inserted.
Continuous data is expressed as the mean ± standard deviation and range.

3. Results

A total of 268 patients received intravenous amiodarone during the period from January 2014 to August 2016. The details of the study group are provided in Table 1. There were 152 males and 116 females, with a mean age of 56 ± 22 years. The indication for IV amiodarone was monomorphic ventricular tachycardia in 142, atrial fibrillation/flutter in 104, and incessant atrial tachycardia in 22 patients. The mean left ventricular ejection fraction was 43 ± 12%. Underlying heart disease in those who received IV amiodarone for ventricular tachycardia was, coronary artery disease in 96, dilated cardiomyopathy in 22, arrhythmogenic right ventricular dysplasia in 10, sarcoidosis in 8, and hypertrophic cardiomyopathy in 6 patients. In patients who received IV amiodarone for atrial flutter/fibrillation, a chronic rheumatic valvular disease was the underlying etiology in 48, hypertensive heart disease in 26, ischemic heart disease in 16, dilated cardiomyopathy 8, sinus node dysfunction with pacemaker 3 (VVI), and hypertrophic cardiomyopathy in 1 patient.

Out of 268 patients who received IV amiodarone, 4 (1.5%) patients developed TdP. The details of patients who developed amiodarone induced TdP are given in Table 2. There were three females and one male in with a mean age of 51.25 ± 9.17 (range: 43–63) years. The underlying etiology of patients who whom one patient rheumatic mitral stenosis, one sick sinus syndrome with VVI pacemaker, one dilated cardiomyopathy with LVEF 32% and recurrent VT, and one with hypertensive heart disease. The mean dose of amiodarone was 690 ± 176.63 (range: 510–930 mg) mg infused over a period of 12 ± 5.88 (range: 6–20) hours. The mean QTc for all the four patients was 505 ± 9.02 ms (range: 492–512).

Case 1 (Fig. 1) with rheumatic mitral stenosis was being treated with beta-blocker and digoxin resulting in triple therapy and Cases 2 and 4 (Fig. 3) were receiving beta-blocker before initiation of IV amiodarone. On presentation, the patient with sick sinus syndrome and VVI pacemaker (Case 2), the pacemaker had been programmed to 60 bpm with a hysteresis of 45 bpm, to prevent unnecessary ventricular pacing. After defibrillation of TdP, the pacemaker was programmed to 90 bpm for 48 h, to prevent pause dependent TdP. Case 3 had severe left ventricular dysfunction with LVEF of 32% and this patient; fifteen minutes after starting isoprenaline, developed rapid monomorphic ventricular tachycardia/flutter (Fig. 2) with hemodynamic deterioration requiring defibrillation. Isoprenaline was stopped immediately, and temporary pacing was instituted at 90 bpm for 48 h. He was later diagnosed as dilated cardiomyopathy and underwent a successful implantation of an implantable cardioverter defibrillator as a class I indication for secondary prevention. All patients are alive.

Fig. 1. (a) ECG of case 1 showing atrial flutter with a ventricular rate of 150 beats per minute. (b) ECG of case 1 after defibrillation of TdP six hours after IV amiodarone infusion. The sinus rhythm ECG shows marked sinus bradycardia with prolonged QT interval with QTc interval of 500 ms and R on T eptics.
and doing well on follow up of 7 ± 2.1 (range: 5–10) months and the QTc was 433.75 ± 6.13 ms (range: 426–440). None of the patients tested positive for 13 most common genes of long QT syndrome. The three patients whose LV function was normal did not undergo an ICD implantation because the cause of TdP was drug induced and the QTc normalized after stopping the drug. The mean QTc of patients who did not develop TdP was 464 ± 14 ms and was measured in the ECG’s done immediately after patients resumed sinus rhythm.

4. Discussion

The present case series shows the development of hemodynamically unstable drug-induced TdP after IV amiodarone therapy is about 1.5%. None of the patients were on QT prolonging drugs, their serum electrolytes were within normal limits, and patients were amiodarone naïve. Females outnumbered males, suggesting that the arrhythmia is more common in women. In the three patients with atrial arrhythmias, the left ventricular function was normal. In the patient with left ventricular dysfunction, QTc interval was normal at baseline before initiation of therapy. There was no family history of sudden cardiac arrest or LQTS in any of these patients. TdP occurred 6 to 20 h after infusion of IV amiodarone and required defibrillation because it was sustained and caused hemodynamic compromise. The mechanism of arrhythmia was pause dependent TdP, and subsequent sinus rhythm ECG revealed prolongation of QTc in all patients and QTc interval normalized 48 to 72 h after stopping amiodarone and continues to be normal on medium-term follow-up indicating that QTc was normal at baseline. Patient with LV dysfunction developed hemodynamically unstable ventricular flutter with isoprenaline that was started to prevent pause dependent TdP. Two patients required RV pacing for 48 h to prevent recurrent pause dependent TdP. None of the patients tested positive for the 13 common genes for long QT syndrome. One patient was on beta-blocker and digoxin, and two patients were on beta-blockers before amiodarone infusion.

4.1. Epidemiology

There has been an increasing awareness of drug-induced TdP resulting in an in increasing number reports. It has been suggested that the system of spontaneous reporting under-reports the actual incidence of serious adverse reactions by a factor of at least 10.8 Prevention strategies must consider the drug’s toxic potential, route and rate of administration, the dose, actions of any concomitant medicines and any other correctable factors. Intravenous amiodarone has emerged as an important drug for the acute treatment of ventricular tachyarrhythmias, and ventricular rate control in atrial arrhythmias, not responding to other antiarrhythmic agents.2–4 Initially, single case reports of drug-induced TdP hours after initiation of intravenous amiodarone-associated with QT prolongation appeared in the literature.9 In a series patients treated with IV amiodarone for atrial arrhythmias, the incidence of TdP has been reported to be 2.6%.10 In an epidemiological study of drug-induced LQTS from Germany, amiodarone was the most common cause in 10 out of 35 cases. The drug was administered intravenously in half of these patients making.6 Amiodarone-associated TdP has also been reported increasingly in China.11 Amiodarone was the most common cause of drug-induced TdP and was implicated in 54% cases in a study from Singapore, and the drug was given intravenously in nearly half of patients.12 Women appear to be at increased risk of drug-induced TdP in many of the studies.5,10,11 Other risk factors include hypokalemia,11 pretreatment with digoxin,13 triple therapy with beta-blockers, digoxin, and amiodarone,14 and left ventricular dysfunction.15 The hallmark of drug-induced TdP with amiodarone is, prolongation of QTc in patients with normal QTc before initiation, pause dependent onset, polymorphic VT degenerating to VF, and normalization of QTc 48–72 h after drug withdrawal. Rechallenge with the drug has been shown to reinduce prolongation of QT and TdP implicating amiodarone as the causative agent.9 The mortality has been reported to be between 15 and 21.8% in various studies.11,12 In the present series, none of the patients tested positive for genes of long QT syndrome. In a large series of patients with drug-
induced LQT, only 28% tested positive for long QT genes, and these patients could be identified by baseline prolonged QT. 16 With increasing use of amiodarone, it is evident that amiodarone has emerged as the most common cause of drug-induced TdP. 5,6,11,12 TdP associated with IV amiodarone is associated with significant mortality and needs prompt recognition and treatment. 11,12

4.2. Possible mechanism

Chronic oral administration of amiodarone markedly prolongs the QT interval, and yet, it is very rarely associated with TdP. The low incidence of proarrhythmia has been attributed to the increased homogeneity of repolarization in contiguous myocardial cells and the lack of calcium-dependent early after-depolarization. 17 Though not proven, it is postulated that chronic oral amiodarone uniformly delays repolarization in all layers of the myocardial wall. As a result, there is only QT prolongation and no transmural heterogeneity of repolarization, which is the essential substrate for the development of a reentrant arrhythmia. Another theory regarding the low TdP risk nature of amiodarone is that it inhibits the physiological late sodium currents that ultimately produce the arrhythmia. Acutely, IV amiodarone does not prolong ventricular refractoriness, but shows a relatively small but significant slowing of intraventricular conduction and does not prevent inducibility of ventricular tachycardia. 18 The clinical onset of action after IV administration occurs after 1 to 2 h later, both for termination of ventricular arrhythmias, or ventricular rate control of atrial arrhythmias. 2,3 TdP typically occurs 6–24 h after intravenous administration of amiodarone. This could be due to higher drug concentrations and greater cardiac exposure than corresponding oral dosing. Provocative data from an animal model of TdP, suggests that a rapid infusion may be more likely to cause arrhythmia than slower infusion because of higher blood levels. The mechanism underlying this effect is unknown but may reflect differential drug delivery to various sites within the myocardium. 7 Plasma concentrations >2.5 mg/L have been associated with
increased risk of toxicity. Thus, intravenous route of administration may pose an increased risk of TdP compared to oral route. Amiodarone prolongs action potential duration of atrial and ventricular muscle, and delays repolarization. At ventricular level, this prolongation might provoke early after-depolarization and spatial as well as the temporal dispersion of repolarization. This, in turn, induces short-coupled premature ventricular complexes, leading to malignant ventricular tachyarrhythmia. Right ventricular monophasic action potential recording in a patient who developed pause dependent TdP after IV amiodarone has revealed pause-related high amplitude early after-depolarization as the cause supporting the hypothesis. Amiodarone also has reverse use dependence, and bradycardia due to concomitant drugs such as beta blocker and digoxin or triple therapy may potentiate its action. The possible explanation for women being more prone to amiodarone-induced TdP is the decreased repolarization reserve in women making them more sensitive to the proarrhythmic effect.

Unlike other intravenous antiarrhythmic drugs that have a uniform and usually single dosing regimens recommended, the dosing with amiodarone has been varied in various studies.

4.3. Characteristics (Table 3)

TdP after intravenous infusion of amiodarone appears to have certain characteristics that may help in its early recognition, and early treatment. Firstly, TdP with IV amiodarone usually occurs within 24 h after initiation of therapy. Secondly, TdP occurs with prolongation of QT interval within 24 h after initiation. Thirdly, the arrhythmia is typically pause-dependent and starts as TdP degenerating to ventricular fibrillation. Fourthly, once the drug is withheld the QT interval normalizes 48–72 h later. Fifthly, drugs that cause bradycardia such as beta-blockers and/or digoxin, not an uncommon combination, when used concomitantly increase risk of TdP with intravenous amiodarone. Sixthly, electrolyte imbalances such as hypokalemia and hypomagnesemia increase the risk of TdP. Finally, in patients who develop TdP with IV amiodarone, reinitiating the drug under more stable clinical conditions is associated with TdP and is hazardous, and amiodarone should never be given in future. Understanding of these factors may help to create future preventive strategies.

4.4. Limitations

This is a single-center study with a limited number of patients with all its limitations. This finding needs to be confirmed in larger multicenter studies. The dose used has been uniform to result in an infusion of 1 gm/day as recommended and whether the similar findings are seen with other dosing regimens is not known. Whether different intravenous loading regimens of amiodarone have a differing risk for TdP is also not known. However, epidemiological and population-based studies from France, Germany, China, and Singapore has implicated IV amiodarone as the commonest cause of drug induced TdP.

4.5. Implications

Although amiodarone has been considered safe, its arrhythmogenic potential when given intravenously should not be underestimated. The various modifiable and non-modifiable risk factors, and the possible actions necessary to prevent or minimize the risk of TdP are presented in Table 4. Careful ECG monitoring of ECG during the first 24–48 of IV amiodarone infusion is suggested. Electrolyte imbalances that could prolong the QT interval should be looked for and corrected before initiation of therapy. Baseline QTc should be assessed before starting therapy and IV amiodarone should be avoided in patients with baseline QT prolongation. Modification of the drug dose with a lesser dose, and avoidance of bolus dose, with a slower infusion rate, should be considered in females, and in patients with left ventricular dysfunction. For patients who have been on beta-blockers and/digoxin, it may be preferable to avoid initiation of IV amiodarone. Triple therapy with beta-blockers, digoxin, and amiodarone should be avoided. In case it is necessary to give IV amiodarone, it may be better to initiate IV amiodarone after stopping those drugs, with a sufficient washout period, and under careful ECG monitoring. Treatment of drug-induced TdP involves prompt defibrillation, intravenous magnesium, lignocaine infusion, isoprenaline or temporary pacing till QT normalizes. As seen in the present study, use of isoprenaline to increase the ventricular rate, and prevent pause dependent TdP may be hazardous in patients with a history of left ventricular dysfunction and ventricular tachycardia. In patients with left ventricular dysfunction with drug-induced TdP, temporary ventricular pacing may be a better option. Finally, a uniform and safe dosing regimen of IV amiodarone need to be explored.

5. Conclusion

Compared to chronic oral administration, IV amiodarone appears to have a higher incidence of drug-induced TdP with an incidence of approximately 3%. Before initiation of therapy, risk factors that may increase the chance of developing TdP should be looked for and corrected, to reduce the incidence. The prognosis is good once the drug is withdrawn and amiodarone should not be given at any time in future in those who have developed amiodarone-induced TdP with IV amiodarone therapy.
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Conflict of interest

None.

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