Torsade de Pointes in Patients on Chronic Amiodarone Treatment: Contributing Factors and Drug Interactions

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Abstract

Background: Torsade de pointes is rarely associated with chronic amiodarone treatment, despite the effect of amiodarone on QT interval prolongation.

Objective: To identify risk factors and associated conditions that may cause TdP in patients on chronic amiodarone treatment.

Methods: We reviewed the data of six consecutive patients on chronic amiodarone treatment who were admitted to the intensive cardiac care unit due to syncope and TdP.

Results: The patients' median age was 73.5 years, and five were women. Concomitantly, loratadine was given to two patients and trazodone to one patient. Associated and attributing conditions to the development of TdP were hypokalemia in three patients, drug-induced bradycardia in one and reduced left ventricular function in four.

Conclusions: TdP associated with chronic amiodarone treatment may occur when amiodarone is co-administered with drugs that may potentially prolong QT interval. Additional risk factors for amiodarone-associated TdP include female gender, hypokalemia, reduced left ventricular function and bradycardia.

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Torsade de pointes is an arrhythmia known to be provoked by drugs that prolong the QT interval [1]. Although amiodarone markedly prolongs repolarization and may aggravate ventricular tachyarrhythmias in 1–2% of patients, TdP associated with chronic amiodarone treatment is very uncommon [2]. Moreover, the risk factors and associated conditions that may cause TdP in patients on chronic amiodarone treatment are not well elucidated.

TdP = torsade de pointes

Patients and Methods

We reviewed the data of six consecutive patients admitted to our department because of syncope and TdP from April 1997 to August 2004. Data were retrospectively collected from the patients' hospital files as well as from reviewing the data from the files of each treating family physician. In addition, we performed an English-language literature search (PubMed) for the association of amiodarone with TdP. Series of patients and case reports were reviewed for concomitant medications, predisposing factors, QTc interval length, presenting symptoms, and the type of arrhythmia treated with amiodarone.

Results

All patients were on chronic amiodarone treatment at a daily dose of 200 mg for a period longer than 1 month (average 4 months), and all patients presented with syncope. Table 1 presents the clinical characteristics as well as associated conditions and additional drugs known to prolong QT interval in these patients. The patients' median age was 73.5 years. Most patients (n=5) were women. Amiodarone was administered for atrial fibrillation in five patients and recurrent ventricular tachycardia in one. Their serum magnesium and calcium were within the normal range except for patient no. 6, whose serum magnesium was low (1.53 mEq/L). This was the only patient with left ventricular hypertrophy on transthoracic

Table 1. Patients' clinical characteristics

No.	Age (yrs)	Gender	Chronic arrhythmia	Associated disease	LVEF (%)	Potassium (mmol/L)	QT_c (msec)	L-S	Rate (bpm)	Additional drug	TdP onset*
1	73	F	VT	HTN, HLP	60	4.5	600	Yes	60	Loratadine (10 mg/day)	2 days
2	75	M	PAF	CAD, HTN, DM, HLP	40	3.8	600	Yes	51	Atenolol (25 mg/day)	35 days
3	68	F	PAF	CAD, HLP	40	3.0	560	Yes	62	None	_
4	71	F	PAF	CAD, DM, HLP	30	2.7	480	No	70	Trazodone** (50 mg/day)	2 months
5	74	F	PAF	CAD, DM	40	4.4	500	No	66	Loratadine (10 mg/day)	7 days
6	77	F	PAF	HTN	60	2.16	600	Yes	65	Atenolol (25 mg/day)	3 weeks

* Time from additional drug therapy

** In this patient amiodarone was added to chronic trazodone therapy (2 years)

bpm = beats per minute, CAD = coronary artery disease, DM = diabetes mellitus, HTN = arterial hypertension, HLP = hyperlipidemia, LVEF = left ventricular ejection fraction, PAF = paroxysmal atrial fibrillation, L-S = long-short sequence, VT = ventricular tachycardia.

Table 2. Patients' characteristics of the reviewed series

Author [ref]	N	Median age (yrs)	Female patients	QTc (msec)	Predisposing factors				Syncope	Treated arrhythmias		
					Bradycardia	CHF	Hypokalemia	Concomitant drugs (n)		AF	VPBs	Recurrent VT
Sclarovsky et al. [3]	5	68	4	–	1	3	2	–	3	1	2	1
Tong et al. [4]	7	76	4	537 ± 96	1	4	2	Flecainide (1), diltiazem (1)	6	5	1	1
Faber et al. [5]	2	66	1	521 ± 44	1	1	–	Sotalol (1)	2	1	–	1
Brown et al. [6]	5	69	5	616 ± 61	–	–	2	Digoxin (4)	5	4	1	–
Case reports [7–11]	5	60	3	557 ± 48	1	2	–	Digoxin, procainamide (1)	3	3	1	1
Antonelli et al. (present study)	6	73.5	5	556 ± 54	1	4	3	Loratadine (2), trazodone (1), atenolol (2)	6	5	–	1
Total	30	68.5	22	557 ± 36	5	14	9	13	25	19	5	5

AF = atrial fibrillation, CHF = congestive heart failure, N = number of patients, QTc = corrected QT interval, VPBs = ventricular premature beats, VT = ventricular tachycardia.

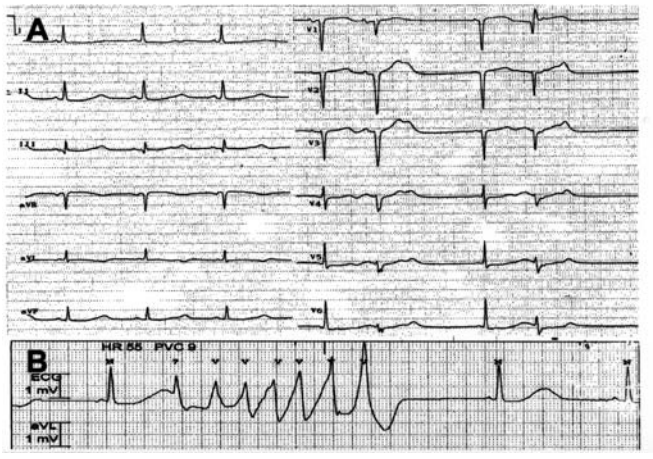

Figure 1 [A] Admission 12-lead ECG (patient no. 1) showing sinus bradycardia, long-short QRS cycle, multifocal ventricular premature beats, QT 720 msec, QTc 688 msec. **[B]** Rhythm strip showing sinus bradycardia, long QT interval, and a long-short QRS cycle preceding one of multiple episodes of TdP on the day of admission

echocardiography. Three patients had hypokalemia, one had drug-induced bradycardia and four had reduced left ventricular systolic function. In two patients TdP occurred 2 days after ingestion of 10 mg/day loratadine [Figure 1], and in one patient 2 months after adding amiodarone to chronic therapy with trazodone 50 mg/day. Long-short sequence was present in four patients. All the patients were discharged alive. However, patient no. 3 died of congestive heart failure 8 months after discharge.

Table 2 summarizes the findings of the English literature review in addition to our series [3–11]. Thirty patients, median age 68.5 years, were analyzed; 22 (73%) were women, and the mean QTc SD was 557 ± 36 msec. Bradycardia was reported in 5 patients (17%), congestive heart failure in 14 (47%), hypokalemia in 9 (30%) and concomitant drugs in 13 (43%). Syncope was the presenting symptom in 25 patients (83%) and atrial fibrillation was the result of amiodarone treated arrhythmia in 19 patients (63%).

Discussion

Torsade de pointes and syncope are rarely associated with chronic amiodarone treatment. However, our case series shows that several conditions and risk factors may increase the risk of TdP and syncope in patients on chronic amiodarone treatment: co-administration of drugs that may prolong QT interval, female gender, electrolyte disturbances, bradycardia and reduced left ventricular function.

The electrophysiologic mechanism of TdP is not fully understood. Most data suggest that TdP is caused by calcium-dependent early after-depolarizations [1]. Amiodarone has been shown to reduce or abolish early after-depolarizations. This electrophysiologic property may explain the low incidence of TdP associated with amiodarone (1–2% of chronically treated patients), despite a markedly prolonged repolarization [2]. Amiodarone also blocks the slow inward calcium current mediated through the L-calcium channels, besides its blocking effect of the delayed rectifier current (I_{kr}) and fast sodium current.

Additional drugs and factors may predispose to QT interval prolongation and TdP [12,13]. In our patients, two drugs associated with amiodarone and TdP were not anti-arrhythmic drugs: loratadine and trazodone.

Loratadine, a second-generation antihistamine drug recently suggested to be registered as an over-the-counter drug, does not significantly prolong QT interval and is considered safe [14]. Nevertheless, when administered with nefazodone it prolonged the mean QTc interval [15], and a single case of TdP suspected to be induced by loratadine alone was recently reported [16]. The mechanism associated with the arrhythmia is suggested to be the blockade of the HERG I_{kr} channel in a similar way to terfenadine [17]. In two of our patients on chronic amiodarone treatment, TdP occurred a few days after loratadine administration. This prompted us to advise electrocardiogram monitoring after ingestion of the first dose of loratadine when it is added to drugs that may potentially prolong QT interval [18].

Trazodone, a second-generation tricyclic antidepressant, has been associated with few cardiac side effects. However, prolonged QT interval due to an overdose of trazodone, and a case of TdP associated with a co-administration of trazodone and amiodarone

have been reported [19,20]. In our patient (no. 4), apart from the trazodone-amiodarone combination, the presence of hypokalemia may have contributed to the occurrence of TdP.

Bradycardia is a condition that can induce early after-depolarizations and facilitate TdP onset [21,22]. It was present in one patient in our series (due to atenolol) and in the series of Tong et al. [4] (due to diltiazem). In another series four patients received digoxin, but bradycardia was not observed [6]. Digoxin toxicity may initiate delayed after-depolarization-triggered activity. However, digoxin serum level was in the normal range in all the patients. Moreover, no case of TdP due to digoxin alone was ever reported. We believe that concomitant digoxin administration may be a facilitating factor of TdP onset only when it causes bradycardia, as in a case reported by McComb and colleagues [8]. In our series, bradycardia was present in an additional two patients and was probably induced by the beta-blocking effect of amiodarone itself.

It has previously been indicated that the combination of hypokalemia and amiodarone is hazardous [23]. Indeed, in our series it was also frequently associated with TdP, having been found in one-third of the patients. We therefore recommend that potassium serum levels be thoroughly monitored and hypokalemia avoided in patients on chronic amiodarone treatment.

In conclusion, amiodarone alone infrequently induces TdP. However, as emerges from our series, the risk factors for amiodarone-induced TdP include the co-administration of additional drugs that may potentially prolong the QT interval, in addition to female gender, bradycardia and hypokalemia.

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