Amiodarone-induced torsade de pointes in a child with dilated cardiomyopathy

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Dilated cardiomyopathy; Electrocardiography; Pediatric age; QT dispersion; Torsade de pointes.

Amiodarone has a high incidence of side effects, but few pro-arrhythmic effects. We report a case of amiodarone-induced torsade de pointes in a child aged 10 years. The patient had severe dilated cardiomyopathy, and even though he was treated with low oral doses of amiodarone, without dosage increments and electrolyte imbalance, he developed torsade de pointes at nights, after T-wave modification and increases of the corrected QT interval (QTc, 20%), QT dispersion (QTd, 175%) and QTcd (116%). The arrhythmic events were preceded by sinus bradycardia at Holter monitoring. Amiodarone therapy was discontinued. Intravenous magnesium administration was not effective in the suppression of torsade de pointes. High-rate atrial pacing prevented recurrences of the arrhythmias and reduced the QTc interval by 20%, QTd by 50%, and QTcd by 70%; QTd and QTcd returned below normal limits. This case underscores the need of careful electrocardiographic monitoring during amiodarone therapy.

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Introduction

Amiodarone is an excellent, class III antiarrhythmic agent which is effective in the treatment of supraventricular and ventricular tachyarrhythmias and is widely used in adult and pediatric patients. Although amiodarone has a high incidence of side effects[1], it is relatively safe and appears to have few pro-arrhythmic effects when it is properly administered. Torsade de pointes is a polymorphic ventricular tachycardia associated with congenital or acquired QT interval prolongation. Acquired QT interval prolongation is caused either by electrolyte abnormalities or drugs, especially class Ia and III antiarrhythmic agents. In pediatric age, only a few cases of amiodarone-induced torsade de pointes are reported. The present case report deals with the pro-arrhythmic effects of low oral doses of amiodarone.

Case report

The patient, a 10-year-old child (height 136 cm, weight 28 kg, body surface area 1.04 m^2), presenting with dyspnea and ortopnea 2 weeks after a fever episode, was hospitalized and dilated cardiomyopathy with frequent, non repetitive, premature ventricular complexes was diagnosed. The ECG before amiodarone therapy (Fig. 1, Table I) showed sinus rhythm, left ventricular hypertrophy, a corrected QT (QTc) interval of 0.45 s1/2, QT dispersion[2] (QTd) of 40 ms and QTcd of 60 ms. He was treated with captopril and amiodarone, 200 mg/day, for 5 days per week. Then, he was transferred to our Institution for further evaluation. Echographic examination showed a severe dilated cardiomyopathy. The left ventricular end-diastolic diameter, end-diastolic volume and end-systolic volume were 64 mm, 150 ml and 120 ml respectively. The ejection fraction was 20%. Mild mitral and tricuspid regurgitation was present and the right ventricular systolic pressure was 30 mmHg. The ECG (Fig. 2, Table I) at admission (January 31, 1999) showed sinus rhythm, a vertical QRS axis, left ventricular hypertrophy, flat T waves in the precordial leads, a QTc interval of 0.45 s1/2, QTd of 40 ms, QTcd of 60 ms. Standard ECG was recorded at 25 mm/s (HP Page Writer XLi). We determined the end of the T wave at the return to the baseline; when this was not possible, such as during high-rate atrial pacing, the end of the T wave was identified at the intersection of the tangent to the down-slope of the T wave with the isoelectric baseline. QT correction was performed according to Bazett's formula. Amiodarone therapy was continued at the same dosage. Some days later, the

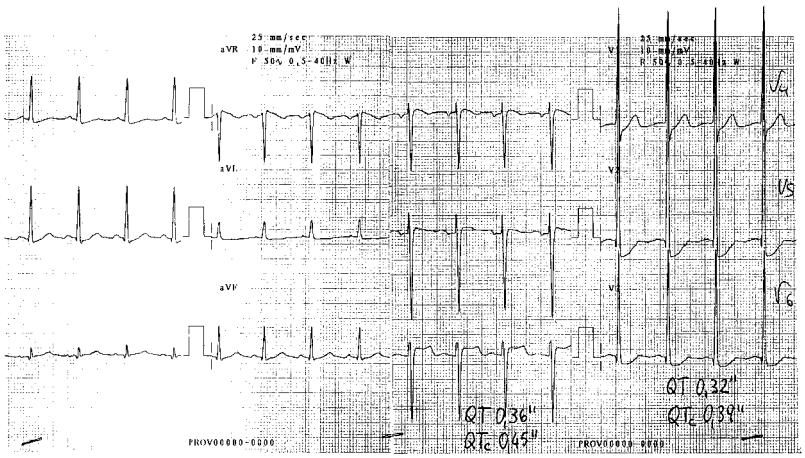

Figure 1. *The ECG before amiodarone therapy.*

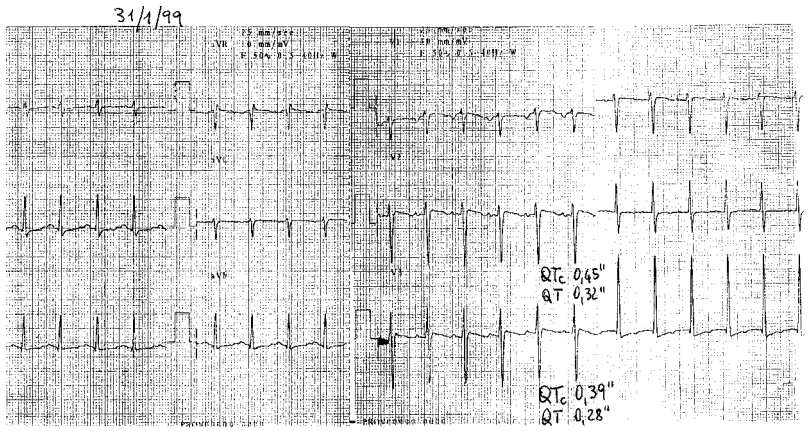

Figure 2. *The ECG at admission.*

Table I. Repolarization parameters in the ECG of the child.

	CL (ms)	QT (s1/2)	QTc (s1/2)	QTd (ms)	QTcd (ms)
No amiodarone	640	0.36	0.45	40	60
Admission	510	0.32	0.45	40	60
Day of torsade de pointes	750	0.48	0.56	110	130
Amiodarone discontinuation	750	0.52	0.60	80	110
Atrial pacing	500	0.34	0.48	40	50

CL = cycle length; QTc = corrected QT; QTd = QT dispersion.

boy had syncope and near syncope with dizziness, impaired consciousness and convulsions, during the night. The ECG (February 5, 1999) showed (Fig. 3) T wave inversion in the precordial leads, a QTc interval of 0.56 s1/2, QTd of 110 ms, and QTcd of 130 ms (Table I).

Twenty-four hour Holter monitoring (February 5-6, 1999) (Oxford Medilog Excel, Oxford Medical Instruments, Abingdon, UK) showed severe sinus bradycardia, frequent and repetitive premature ventricular complexes triggering episodes of torsade de pointes (maximum duration 2 min) associated with the symptoms described, with a higher prevalence at 2.00 a.m. (Fig. 4, Table I). The torsade de pointes was generally self-terminating, except in some episodes, when the patient was defibrillated.

No electrolyte abnormalities were present (on the day of the event the plasma potassium concentration was 4.6 mEq/l whereas that of calcium was 9 mg/dl). Amiodarone therapy, which lasted less than 3 weeks, was discontinued; magnesium sulfate was administered intravenously but no significant benefits were observed.

Under local anesthesia, a temporary pacing electrode was inserted into the right femoral vein and positioned within the right atrium. The patient was paced at 110-130 b/min. Without atrial pacing, the ECG showed a QRS axis shift (+30°), positive T waves in V_1-V_3, a QTc interval of 0.60 s1/2, QTd of 80 ms and QTcd of 110 ms (Fig. 5). During pacing, the repolarization parameters shortened: QTc 0.48 s1/2, QTd 40 ms, QTcd 50 ms (Fig. 6, Table I). This therapy effectively prevented torsade de pointes.

In the following days, ECG showed a progressive reduction in repolarization abnormalities; Holter moni-

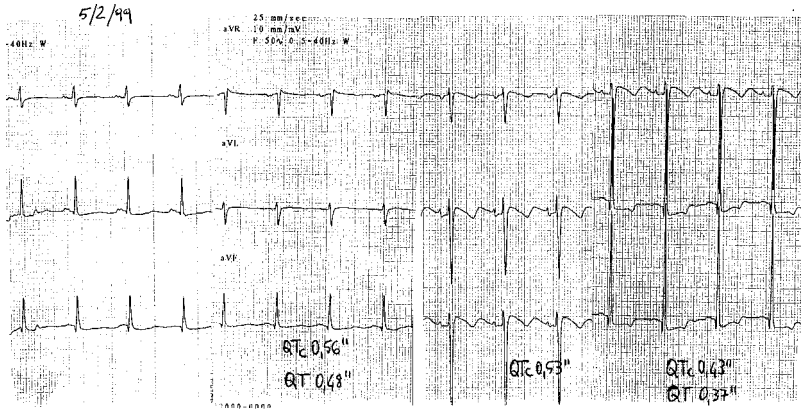

Figure 3. *The ECG on the day of torsade de pointes.*

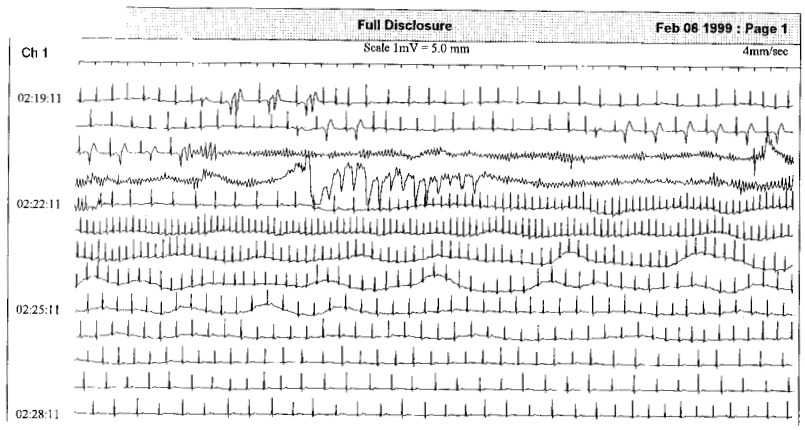

Figure 4. *Torsade de pointes at Holter monitoring.*

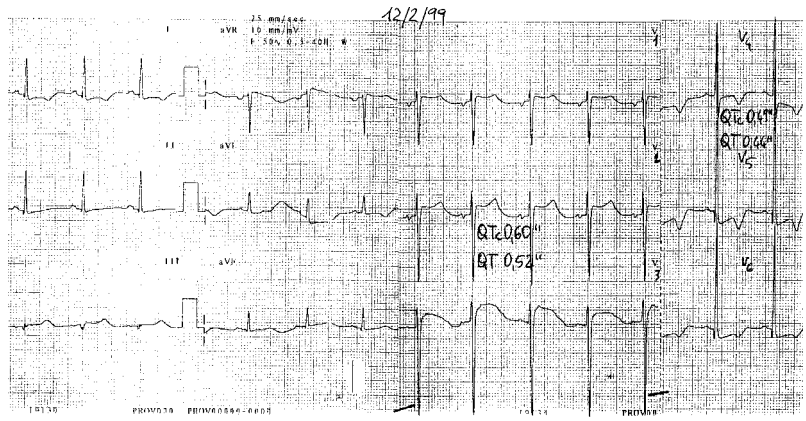

Figure 5. *The ECG in the absence of atrial pacing after amiodarone discontinuation.*

toring revealed non repetitive premature ventricular complexes and torsade de pointes did not recur.

Late potentials (HP Page Writer XLi) were absent (QRS duration 87 ms, RMS 265 μV, RMS40 281 μV, LAS 5 ms). The patient was also treated with inotropic drugs, captopril, diuretics, oral anticoagulants, cortisone and immunosuppressants. In spite of a history suggestive of previous myocarditis, cardiac catheterization and endomyocardial biopsy were not performed owing to the high anesthetic risk.

In order to exclude a forme fruste of long QT syndrome, the ECGs of first degree relatives have been registered, and showed borderline QTc intervals. The father's ECG revealed: QTc 0.44 s1/2, QTd 20 ms, QTcd 10 ms (Fig. 7). The mother's ECG revealed: QTc 0.45 s1/2, QTd and QTcd 50 ms (Fig. 8). The family history did not in-

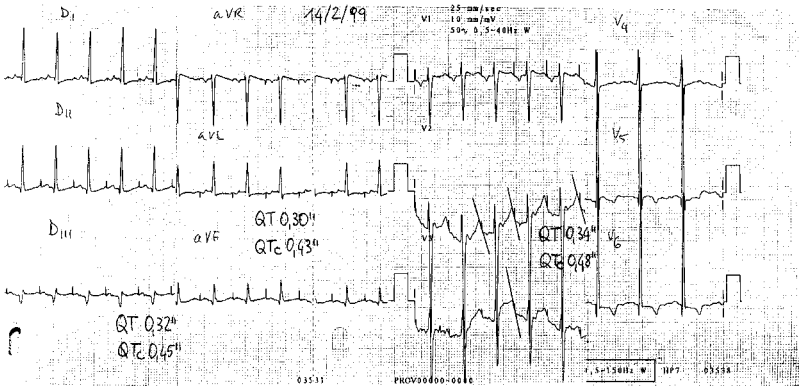

Figure 6. *The ECG during high-rate atrial pacing.*

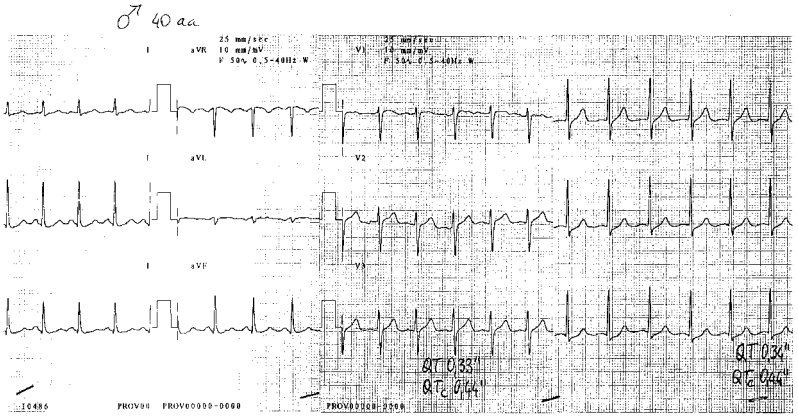

Figure 7. *The ECG of the child's father.*

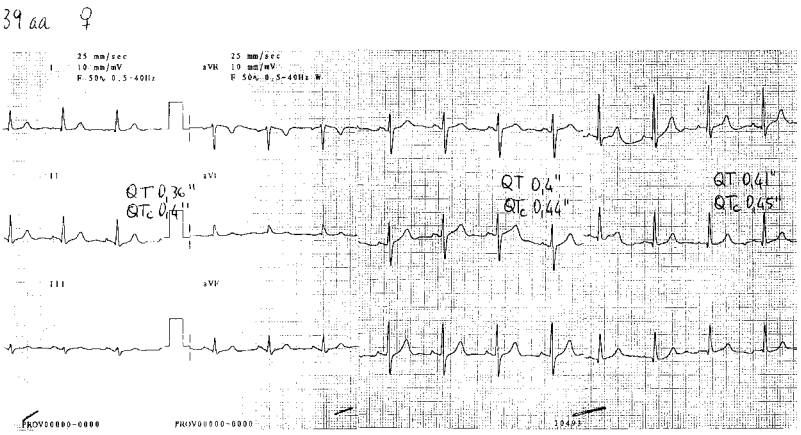

Figure 8. *The ECG of the child's mother.*

clude sudden cardiac death. Unfortunately, we do not have an ECG of the child before manifestation of the severe form of dilated cardiomyopathy, and we do not know if a borderline QTc was already present at baseline.

The patient was discharged in stable conditions. Dyspnea, palpitations, dizziness and syncope were absent. During follow-up lasting 12 months, no symptoms recurred and the child was hemodynamically stable; echography did not show significant improvement and at Holter monitoring only frequent, isolated and monomorphic premature ventricular complexes were found. He is waiting for heart transplantation.

Discussion

Amiodarone prolongs refractoriness and increases action potential duration by blocking the delayed rectifi-

er current Ik. It also has class I, II and IV properties. Its pharmacokinetic properties account for the delayed onset of clinical effects, although electrophysiologic effects may develop within 1-2 days. The usual pediatric oral loading dose is 10-15 mg/kg/day for 5-10 days, followed by 2-5 mg/kg/day[3].

A review of the literature[4] shows overall incidences of 2 and 0.7% for pro-arrhythmic events and torsade de pointes respectively. Other authors report an incidence of 1-2% for torsade de pointes[1,3]. For this reason, except in case of advanced heart failure[5], amiodarone is safe even in patients with previous drug-mediated torsade de pointes[4,6,7] despite similar QTc interval prolongation. Torsade de pointes occurs more frequently in women[8], and predisposing factors are hypokalemia or the association with other antiarrhythmic class Ia drugs or dosage increments. Torsade de pointes is described even early after initiation of low-dose oral therapy in the absence of other predisposing factors[9].

The low incidence of torsade de pointes, despite considerable lengthening of the QTc interval and substantial bradycardia during amiodarone therapy, could be due to a decrease in QTd associated with lengthening of repolarization[1,6,10], to the abolition of calcium-dependent early afterdepolarizations, to a much shorter prolongation of repolarization in Purkinje fibers than in ventricular muscle[4,10] or to suppression of ventricular ectopy which often precedes torsade de pointes[7]. Generally, the relationship between the degree of QT lengthening and the development of torsade de pointes is not linear[10]. Besides, no critical QT duration has been identified[7]. Indeed, just before the occurrence of torsade de pointes, the QTc interval is highly variable[11].

Intravenous and oral amiodarone is effective and safe for the treatment of resistant, life-threatening arrhythmias in infants and children[12-15]. Only few pediatric studies report pro-arrhythmic events or torsade de pointes[16,17] during amiodarone therapy. In our previous experience, no pro-arrhythmic event was observed[18].

This case deserves some considerations. The patient began amiodarone therapy at another Institution for non repetitive premature ventricular complexes. The dosage was low (< 7 mg/kg for 5 days a week) and therapy lasted less than 3 weeks. In the absence of repetitive arrhythmias, we usually do not treat such patients with amiodarone, even though opinions regarding this point differ. In reality, this child could have died because of a side effect.

The measurement of the QT interval in the ECG registered at a paper speed of 25 mm/s could be influenced by intra and interobserver variability, but this is the standard ECG registration in clinical practice.

In children with congenital long QT syndrome, the increase in QTd and QTcd is associated with the presence of critical ventricular arrhythmias, with cut-off values ranging between 55[19] and 100 ms[20].

In this patient, torsade de pointes occurred when heart rate decreased (with an almost 50% increase in sinus cycle length), the QTc interval exceeded normal limits by 20%, and the QTd and QTcd were markedly prolonged (175 and 116%, respectively), much more than published limits.

High-rate atrial pacing shortened the QTc interval, QTd and QTcd by 20, 50 and 70% respectively, and values of dispersion returned below normal limits. Thus, reduction of QTd and QTcd and the prevention of severe bradycardia, that could further increase these parameters, seemed the most effective treatment for this patient. Moreover, it is important to underscore that, although the onset of drug-induced bradyarrhythmias is not generally considered as a pro-arrhythmic response, such an effect is a real manifestation of arrhythmogenicity.

The only known predisposing factors for the development of arrhythmia were the recent initiation of amiodarone therapy and the presence of congestive heart failure. The presence of structural heart disease was strongly associated with quinidine syncope in children[21].

In conclusion, although generally safe, low-dose oral amiodarone therapy in pediatric patients with severe heart failure and without predisposing factors (electrolyte abnormalities, dosage increases, drug combinations) can induce torsade de pointes. Careful monitoring of the QT, QTc and QTd is mandatory. Therapy should be discontinued when prolongation of these parameters occurs. In our patient, atrial pacing suppressed the arrhythmias.

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