Probucol-induced QT Prolongation and Torsades de Pointes

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Probucol administration of 4 weeks produced torsades de pointes associated with exacerbated QT interval prolongation in a 36-year-old woman with Romano-Ward syndrome. With discontinuance of probucol, the QT interval corrected for rate shortened from 620 msec to 500 msec and ventricular ectopic beats disappeared completely. Although probucol is known to prolong the QT interval, associated ventricular tachyarrhythmia has not been reported in humans as yet. This case suggests that one should be very careful in the administration of probucol to patients with long baseline QT intervals.

Key words: Ventricular tachycardia, Romano-Ward syndrome, QT interval, WPW syndrome, Electrophysiological study

Probucol, a cholesterol-lowering agent that has been useful in the treatment of hypercholesterolemia, is known to prolong the QT interval in some patients. However, associated ventricular tachyarrhythmia has not been reported in humans. We present a case of "torsades de pointes" ventricular tachycardia associated with exacerbated prolongation of the QT interval due to probucol in a patient with Romano-Ward syndrome and WPW syndrome.

CASE REPORT

A 36-year-old woman was admitted on June 10, 1986, with a 10-day history of increasing palpitation and associated syncopal attack. Because of hypercholesterolemia (340 mg/dl), probucol, 750 mg/day, had been given for 4 weeks prior to her admission.

On admission, the physical examination revealed no abnormalities except for the pulse, which was irregular at about 60 beats per minute. The blood pressure was 120/80 mmHg. The electrocardiogram showed frequent premature ventricular beats including short runs, shortening of the PR interval with initial delta wave (type A WPW syndrome) and marked prolongation of the QT interval. The QT interval corrected for rate (QTc) was 620 msec (Fig. 1A, B). Chest X-ray film revealed no cardiomegaly. Serum potassium, calcium, magnesium levels and thyroid profiles were normal.

On the first hospital day, "torsades de pointes" ventricular tachycardia with syncope occurred, which lasted for 40 seconds, and terminated spontaneously (Fig. 1C). In spite of the emergent treatment with ventricular pacing and propranolol administration, a similar attack recurred on the next day. Probucol had been discontinued on admission, after which ventricular ectopic activities gradually disappeared as QTc became shorter. QTc at the 40th hospital day was 500 msec without propranolol (Fig. 2).

Echocardiogram, cardiac catheterization data and coronary arteriogram revealed no evidence of organic heart diseases. Although an electrophysiological study showed the presence of Kent Bundle (effective refractory period, 330 msec), the ventriculo-atrial conduction was absent and supraventricular tachyarrhythmia including atrial
Torsades de Pointes Induced by Probucol

Fig. 1A, B. Complete 12-lead electrocardiogram on admission under probucol treatment. Note a prolonged QT interval, shortening of PR interval with initial delta wave (A) and frequent ventricular premature complexes (B).

Fig. 1C. "Torsades de pointes" recorded on the first hospital day (CM5 lead). The R-R intervals are almost regular (ventricular rate of about 280 per minute) and phasic variation in the electrical polarity of the QRS complex is evident.

Fibrillation was not induced by programmed atrial extrastimulus.

The electrocardiograms of her mother, two siblings, daughter, and son revealed a long QT interval (QTc > 460 msec) without initial delta waves. The most probable diagnosis was congenital long QT syndrome (Romano-Ward syndrome).

The patient was discharged with propranolol, 30 mg/day. She had had no recurrence of palpitation and syncope, and there had been no evidence of ventricular ectopic activities on ambulatory electrocardiograms during 24 months of follow-up.

DISCUSSION

This patient had two problems; Romano-Ward syndrome and WPW syndrome. It was not certain whether the tachyarrhythmia was ventricular tachycardia or supraventricular tachyarrhythmia due
to WPW syndrome. The possibility of supraventricular reentrant tachycardia, however, was virtually excluded following the electrophysiological study. Considering the effective refractory period in this case (330 msec), the tachyarrhythmia (ventricular rate of about 280 per minute) was unlikely to be atrial fibrillation. Furthermore, by the morphological characteristics of the QRS complexes, we diagnosed it as “torsades de pointes” ventricular tachycardia associated with QT prolongation.

In animals such as monkeys and dogs, administration of probucol (mixed into an atherogenic diet) resulted in marked prolongation of the QT interval, and some animals died, apparently of ventricular arrhythmias (1, 2). Probucol increased ventricular effective refractory period in open-chest monkeys (1) and it sensitized canine myocardium to develop ventricular fibrillation after adrenergic stimulation (2, 3), whereas microscopic evaluation revealed no significant changes (4). These studies suggest that the QT interval prolongation may be related to the changes of the myocardial repolarization and the arrhythmogenic mechanism may be related to the facilitation of reentry. However, the mechanisms remain still unknown in detail.

In humans, the drug prolongs the QT interval possibly in a serum concentration-dependent fashion, but does not increase the number of premature ventricular beats or ventricular tachyarrhythmias in patients with normal QT intervals prior to probucol treatment (5-7). This species difference in cardiovascular toxicity potential between man and animal has been accounted for by the differences in pharmacokinetic behavior (very poor bioavailability gastrointestinal absorption in man) (5) and lipoprotein fractions (4).

The adverse effect on a patient with a long baseline QT interval has not been reported as yet. Romano-Ward syndrome is a heritable disorder characterized by a marked propensity for syncope and sudden death due to ventricular tachyarrhythmias (8). Baseline QTc was prolonged (500 msec, modified by delta wave) also in this case. However, her episodes of torsades de pointes seemed to be induced by probucol rather than occurring in a spontaneous manner only, because: 1) She had had no syncopal attack before probucol treatment, 2) with discontinuance of probucol, ventricular ectopic activities disappeared showing gradual shortening of the QT interval. Although the serum probucol level was not obtained it was unlikely to be very high, considering her given dose. Patients with long
baseline QT intervals seem particularly susceptible to this probucol-induced adverse effect.

This case suggests that one should be cautious in administering this drug not only to the patients with long baseline QT intervals but also to the patients who receive other medications that may prolong the QT interval. ECG should be checked before and during the treatment in such cases.

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