PROBUCOL-INDUCED QT PROLONGATION AND SYNCOPE

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We report a patient who experienced a reversible prolongation of the QT interval and episodes of syncope while receiving probucol. A 64-year-old woman experienced syncopal attacks 8 and 11 weeks after beginning probucol treatment (500 mg twice daily). The pre-treatment ECG showed a slight prolongation of the corrected QT interval (QTc) (0.46 sec). Her QTc increased to 0.62 sec 12 weeks after beginning probucol treatment and decreased to about the baseline value (0.48 sec) 6 weeks after treatment was discontinued. Probucol is known to prolong the QT interval. A long QT interval has been linked to an increased risk of ventricular arrhythmias, syncope or sudden death. However, clinical reports which causally relate probucol treatment to syncope are very rare. Although an ECG during the episodes of syncope was not available, this patient’s syncope might be due to ventricular tachyarrhythmia associated with probucol-induced QT prolongation. This case emphasizes the need for careful evaluation of the QT interval before and during probucol treatment.

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PROLONGATION of the QT interval has been associated with a high risk of ventricular arrhythmias, syncope or sudden death! Probucol, a cholesterol-lowering drug, has been linked to prolongation of the QT interval and sudden death in animals? Probucol prolongs the QT interval clinically?–^ but malignant ventricular arrhythmia or syncope due to the drug is very rare? In this report we describe a patient who experienced a reversible QT prolongation with recurrent syncope while receiving probucol.

CASE REPORT
A 64-year-old woman was admitted to our hospital on April 30, 1991, for evaluation of syncope. She had been taking probucol (500 mg, two times daily) and diltiazem (30 mg, three times daily) since February 6, 1991, because of hypercholesterolemia (330 mg/dl) and recurrent paroxysmal atrial fibrillation. She had experienced two episodes of syncope on April 5 and 25, 1991. Both episodes occurred when she was alone at home in the afternoon. She experienced the first episode of syncope when she was attempting to urinate and the second while telephoning a friend. She was warned of the impending faint by a sense of dizziness, and then fell to the floor. Unconsciousness appeared to last about 30 sec, and she felt nauseous after she recovered consciousness.

She had never displayed syncope or other neurological symptoms before these episodes, and she had no family history of syncope or sudden death. Physical examination

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on admission revealed a blood pressure of 132/80 mmHg and a pulse of 60 beats/min. Echocardiogram and chest X-ray findings were unremarkable. Her lipid profile revealed (in mg/dl): total cholesterol, 229; high-density lipoprotein, 29; and triglycerides, 135. The results of other laboratory tests including blood cell count, blood chemistry, thyroid hormone levels and immunology were within normal limits. An ECG performed 8 days before the initiation of the drug treatment showed normal sinus rhythm with an RR interval of 0.66 sec and a slight prolongation of the corrected QT (QTc) interval (0.46 sec) (Fig. 1A). In contrast, an ECG on admission showed that both the RR
interval and the QTc interval had increased (to 0.80 sec and 0.62 sec, respectively) with inverted or biphasic T waves in leads V1-4 and occasional supraventricular premature beats (Fig. 1B). Furthermore, prolongation of the QT interval was accentuated by a short-long cycle sequence (cf the QRS complexes noted by letters “a” to “d” in Fig. 1C). The QTc interval was 0.62 sec for the basic sinus cycle length of 0.80 sec (interval between “a” and “b”). However, an increase in the RR interval to 0.88 sec (interval between “c” and “d”) following a supraventricular premature beat (“c”) resulted in a prolongation of the QTc interval to 0.66 sec. Both probucol and diltiazem were discontinued. Thereafter, the QT interval gradually decreased and the T waves in the precordial leads became upright (Figs. 1D and E). The plasma concentration of probucol on the day of admission (16.0 μg/ml) was within the therapeutic range. Sequential QTc intervals and plasma concentrations of probucol during the following 4 months are presented in Fig. 2. Forty days after the drugs were discontinued, the QTc interval decreased to near the pre-treatment value (0.48 sec), and the plasma probucol level fell to 5.3 μg/ml. The plasma probucol level continued to decrease rather slowly as time elapsed, whereas the QTc interval remained almost unchanged. Linear regression analysis revealed a highly significant relationship between the two parameters: Y=0.429+0.011X, r=0.91, n=17, p<0.001, where X and Y are the plasma concentration of probucol (μg/ml) and the QTc interval (sec), respectively. Syncope did not recur during the 4 month follow-up. Twenty-four-hour ECG recordings were obtained at 2 and 30 days after discontinuing the drugs, and both showed frequent supraventricular premature beats and infrequent ventricular premature beats (7 and 15 per 24 h, respectively) with no ventricular tachycardia. ECG recordings were available from two of the patient’s living family members: the QTc interval was prolonged in her 59-year-old sister (0.48 sec), but was normal in her 45-year-old daughter (0.40 sec).

DISCUSSION

Our patient experienced a reversible prolongation of the QT interval with episodes of syncope while receiving probucol and diltiazem. QT prolongation associated with probucol treatment has been well documented,2-4 whereas, to our knowledge, no such effect has been reported for diltiazem! Accordingly, probucol was most likely responsible for the increased QTc interval in
our patient. There are at present no data which causally relate probucol-induced QT prolongation to an increased incidence of ventricular arrhythmias, syncope or sudden death in patients with a normal QT interval prior to probucol treatment\(^2\)\(^-\)\(^4\). Our patient showed a slightly prolonged QTc (0.46 sec) even before the initiation of probucol, and her sister also showed a prolonged QTc interval (0.48 sec). These findings may suggest a hereditary basis for QT prolongation in her family, i.e., Romano-Ward syndrome. Matsuhashi et al\(^5\) reported a patient with Romano-Ward syndrome who experienced torsade de pointes and syncope associated with an extreme QT prolongation induced by probucol treatment. Although an ECG during the episodes of syncope was not available in our patient, ventricular tachyarrhythmias associated with probucol-induced prolongation of the QT interval may be the mechanism by which syncope occurred.

Our patient experienced syncopal attacks twice at about 8 and 11 weeks after the initiation of treatment with probucol and diltiazem. Previous clinical observations suggest that in approximately half of the patients who develop torsade de pointes during therapy with class I antiarrhythmic agents, arrhythmia will occur within the first 4 days of therapy! Torsade de pointes occurring after weeks or months of asymptomatic therapy has been linked to hypokalemia, hypomagnesemia and bradycardia! It is unknown whether our patient had hypokalemia or hypomagnesemia when she developed syncope. We can speculate that a decrease in heart rate due to diltiazem and the short-long cycle sequence following supraventricular premature beats (Fig. 1C) may have enhanced the QT interval prolongation and the development of torsade de pointes. On the other hand, we should also consider the possibility that syncope in our patient might be related to supraventricular tachyarrhythmias, because such arrhythmias can cause syncope and sudden death\(^6\)\(^,\)\(^7\) and the present patient had frequent supraventricular premature beats with a history of paroxysmal atrial fibrillation.

Previous reports have shown that patients with high plasma concentrations of probucol exhibit greater increases in the QT interval than patients with low concentrations\(^2\)\(^-\)\(^4\). In the present patient, sequential measurement of the QT interval and plasma probucol concentration after the discontinuation of probucol revealed a striking parallel in the time course of changes in these two parameters (Fig. 2).

This case clearly emphasizes the need for careful evaluation of the QT interval before probucol treatment, since probucol-induced QT prolongation may be associated with a high risk of malignant ventricular arrhythmias, syncope or sudden death in patients with a prolonged QT interval on the baseline ECG.

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REFERENCES