Provocative testing and drug response in a patient with the long QT syndrome

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Abstract
A girl of 14 with the long QT syndrome (LQTS) and torsades de pointes is reported. Isoprenaline or adrenaline infusions induced torsades de pointes and inversion of the TU wave. Changes in the TU wave during isoprenaline infusion were used to select effective drugs to treat this patient. A β blocker and calcium channel blocker were selected and the patient had no episodes of syncope for two years. This electrocardiographically guided method may be useful for selecting effective drugs in patients with the LQTS.

Keywords: long QT syndrome, torsades de pointes, isoprenaline.

The idiopathic long QT syndrome (LQTS) is characterised by a prolonged QT interval in the surface electrocardiogram, syncopal episodes, and sudden death caused by ventricular tachyarrhythmia.1-3 We describe a patient with LQTS and torsades de pointes. Infusion of isoprenaline or adrenaline induced TU changes and torsades de pointes. We used TU wave changes during isoprenaline infusion to select an effective drug for this patient.

EXERCISE TESTING
Treadmill testing was performed according to a modified Bruce protocol (fig 1). The protocol stopped when the patient became exhausted. ECG was obtained on a six channel Marquette CASE 12 at a paper speed of 25 mm/s with a calibration of 10 mm/mV. The QT intervals were measured in lead II. Heart rate increased from 70 to 143 beats/min with exercise. QTc was prolonged from 460 ms to 550 ms.

RESPONSES TO ADRENALINE, ISOPRENAline AND METHOXAMINE INFUSION
To examine the influence of alpha and/or beta adrenoreceptor stimulation, adrenaline, isoprenaline, and methoxamine were administered by infusion after we had obtained informed consent from her parents (fig 2). During adrenaline infusion at 0.4 μg/kg/min (alpha and beta stimulation) the QTc interval was prolonged (from 470 ms to 600 ms) and prominent U waves developed especially in lead V3. A bolus injection of adrenaline (0.8 μg/kg) induced inversion of the TU wave in the left precordial leads, multiform premature
ventricular contractions (PVCs), and slow ventricular tachycardia. Infusion of adrenaline (beta stimulation) at the rate of 0.02 μg/kg/min, prolonged the QTc interval (from 480 ms to 590 ms) and induced large U waves. A bolus injection of adrenaline (0.06 μg/kg) was associated with inversion of the TU wave in the left precordial leads and multifurrow PVCs. After bolus injection of methoxamine (40 μg/kg, alpha stimulation) there were increases in blood pressure (from 105/60 mm Hg to 128/82 mm Hg), in QTc interval (from 470 ms to 560 ms), and in U wave amplitude.

ELECTROPHYSIOLOGICAL STUDY

After informed consent was obtained from her parents, we performed an electrophysiological study with the patient fasting, and not sedated. Monophasic action potentials (MAPs) were recorded as previously reported. MAPs were recorded from the right ventricular septum (RVS) and the right ventricular anterior wall (RVA). The duration of MAPs was measured at 90% repolarisation (MAPD90). Adrenaline was infused at the same protocol as described. After drip infusion, the U wave became larger than the T wave and the QT interval was prolonged. MAPD90 increased from 280 ms to 420 ms at the RVS and from 290 ms to 350 ms at the RVA. During drip infusion of adrenaline the patient became uncomfortable. Rapid injection of adrenaline induced torsades de pointes. Humps, which were probably consistent with early afterdepolarisations, were seen immediately before the onset of torsades de pointes (fig 3).
Figure 4 Effects of propranolol and verapamil on preventing the changes in TU produced by isoprenaline. Without such medication QTc was prolonged and U wave amplitude was much increased during isoprenaline infusion. An additional bolus injection of isoprenaline resulted in the inversion of TU waves and premature ventricular contractions. Propranolol prevented the TU alternans waves and suppressed the increase in U wave amplitude during drip infusion of isoprenaline. After bolus injection of isoprenaline premature ventricular contractions were prevented but prominent U waves were observed. Propranolol with verapamil suppressed the TU changes and ventricular extrasystoles more effectively than propranolol alone.

EFFECTS OF PROPRANOLOL AND VERAPAMIL ON TU WAVES

We examined the effects of propranolol and verapamil on the changes in TU induced by isoprenaline (fig 4). Infusion of isoprenaline (0.02 μg/kg/min) induced an increase in U wave amplitude. An additional bolus injection of isoprenaline resulted in the inversion of the TU wave and PVCs. Propranolol (2 mg/kg per day) was given by mouth for 5 days. Two hours after a dose of propranolol the inversion of the TU waves was prevented and the augmentation of the U wave amplitude suppressed during the drip infusion of isoprenaline. Administration of propranolol prevented PVCs but not prominent U waves after a bolus injection of isoprenaline. Next, in addition to propranolol (daily dose of 2 mg/kg), we studied the effect of verapamil (5.5 mg/kg per day). After 5 days of combined treatment the effects of the drugs were tested. The prominent U waves and PVCs after the bolus injection of isoprenaline were significantly reduced.

The effects of propranolol and verapamil on the TU changes induced by treadmill testing were also investigated. Without medication the heart rate was increased from 70 beats per minute to 143 beats per minute with exercise. QTc was increased from 460 ms to 550 ms. After propranolol was given by mouth the heart rate increased from 55 beats per minute to 137 beats per minute with exercise. QTc increased from 500 ms to 550 ms. When propranolol and verapamil were given by mouth the heart rate increased from 54 beats per minute to 128 beats per minute with exercise. QTc was prolonged from 460 ms to 610 ms. The duration of exercise did not change with administration of these drugs. It was difficult to estimate the effects of these drugs by the change in QTc interval or the configuration of TU waves.

This patient continued to receive propranolol and verapamil and has not had a syncope attack for 2 years.

Discussion

In this patient prominent U waves, inversion of the TU wave, PVCs, and non-sustained VT were reproducibly induced by administration of adrenaline or isoprenaline. Beta blockers are effective in 75%–80% of symptomatic patients with idiopathic long QT syndrome. Previously, the effect of drugs has been estimated by their clinical effects. However, in this patient, it was difficult to estimate the drug effect before discharge. Therefore, we used the TU changes to select an effective drug. During drip infusion of isoprenaline, propranolol suppressed the TU changes, but propranolol and verapamil prevented the augmentation of the U wave more effectively.

Figure 3 shows early afterdepolarisations immediately before the onset of torsades de pointes. This suggests a correlation between these two features. When each afterdepolarisations appeared the TU wave became significantly inverted. Morganroth suggested that U waves may represent a summation of early afterdepolarisations occurring throughout the myocardium. Moore reported that early afterdepolarisations may stem from increased inward calcium or sodium currents or from decreased outward potassium current. Early afterdepolarisations may occur when inward depolarising currents exceed outward repolarising currents. In contrast to the normal recovery process, early afterdepolarisations are associated with additional action potentials occurring during the repolarisation process; the rapidly occurring early afterdepolarisations may trigger malignant arrhythmias. These findings suggest that by blocking the calcium current during the repolarisation process, verapamil can suppress the formation of early afterdepolarisations and so abolish TU changes.

A limitation of this report is that we could not document spontaneous torsades de pointes in this patient. We had evidence of only two episodes of syncope, both after emotional stress. We have no evidence that the syncope was caused by torsades de pointes. However, we could induce multiple premature ventricular contractions and TU changes with isoprenaline or adrenaline infusions. Furthermore, propranolol and verapamil prevented multiple premature ventricular contractions and the TU changes induced by isoprenaline or adrenaline infusion.

After starting treatment with propranolol and verapamil she has been free of attack for two years. The electrocardiographically guided selection of the effective drugs may be useful for patients with idiopathic long QT syndrome.
A 65 year old man was free of angina after coronary artery bypass grafting. Angina recurred 57 months later and rapidly worsened over the next 3 months. Coronary and graft angiography was performed and selective angiography of a reversed saphenous vein graft to the obtuse marginal branch of the circumflex showed severe stenoses in the proximal and middle segments of the graft (arrows). The segment between the stenoses contained multiple, mobile, oscillating filling defects suggestive of thrombus (large arrowheads). There are clips on the left internal mammary artery graft (small arrowhead).
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