ADVERSE DRUG REACTION

QT prolongation due to roxithromycin

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Roxithromycin and other macrolide antimicrobials are widely used for a broad variety of infections such as upper respiratory tract infection and community acquired pneumonia. Prolongation of the QT interval, torsade de pointes polymorphic ventricular tachycardia, and sudden death are well described but little known adverse reactions common to all macrolides. We report the case of a 72 year old patient with congestive heart failure caused by ischaemic heart disease who developed severe prolongation of the QT interval after three days of treatment with roxithromycin.

Case report
A 72 year old man presented with severe congestive heart failure. Three months earlier he had been diagnosed with three vessel coronary heart disease with moderately impaired left ventricular function. Thallium scans had failed to demonstrate a distinct area of ischaemia, hence a decision had been made to refrain from surgical treatment. Frusemide (furosemide), digoxin, captopril, and aspirin had been begun because of bradycardia. In view of the impaired left ventricular function, amiodarone was started, instead of β blocker, after recurrent episodes of atrial fibrillation. On admission, the patient was severely dyspnoeic and appeared acutely ill. Physical examination revealed displacement of the apex beat, a prominent third heart sound, coarse rales over both lung fields and pitting oedema of both ankles. The patient was taken to an intensive care unit. Acute myocardial infarction was ruled out and frusemide was begun intravenously. An electrocardiogram (ECG) on admission showed sinus rhythm and incomplete left bundle branch block; QT intervals were normal (QT interval 380 ms, corrected QT interval according to Bazett’s formula [QTc] 390 ms). Roxithromycin (Roussel UCLAF, Romainville, France) 150 mg twice a day was initiated for suspected pneumonia. On the third hospital day, he was transferred to a general medical ward.

On admission there, the patient was generally well with few pulmonary rales and mild pitting oedema of the ankles. An ECG showed new ST depression in the left precordial leads with a markedly negative T wave in V4 (fig 1). The most striking findings, however, were QT and QTc intervals of 680 ms and 660 ms, respectively (fig 1). Serum concentrations of potassium, calcium, and both amiodarone and digoxin were normal. The patient denied chest pain; serum troponin T and creatine kinase were repeatedly normal. Digoxin, roxithromycin, and amiodarone were discontinued and the patient taken to an intermediate care unit to permit continuous ECG monitoring. One week later he was discharged in good health with no dyspnoea and peripheral oedema and with improved QT intervals (QT 460 ms, QTc 430 ms).

Discussion
The QT interval is often neglected during interpretation of the routine ECG. Even measurement of the QT interval is not trivial, particularly when a U wave is also present or when there is gradual transition of the T wave to the baseline. In general, the point at which the downslope of the T wave crosses the baseline can be used to determine the end of the QT interval, although an occasional ECG may still pose difficulties in this regard. Moreover, the QRS width should always be determined to exclude prolongation of the QT interval caused by widening of the QRS interval.

The patient discussed here had a markedly prolonged QT interval after three days in hospital for congestive heart failure. In search of a cause for QT prolongation, inherited and acquired disorders must be considered. Irrespective of the cause, however, markedly prolonged QT intervals confer a high risk of sudden death due to polymorphic ventricular tachycardia, particularly of the torsade de pointes variant. Recent research has elucidated
Box 1: Drugs associated with prolongation of the QT interval

1. Antimicrobial agents
   - Antimalarials (chloroquine, halofantrine, mefloquine, quinine)
   - Macrolides (erythromycin, roxithromycin, azithromycin, spiramycin)
   - Pentamidine
   - Trimethoprim-sulfamethoxazole

2. Drugs with predominant action on the cardiovascular system
   - Class IA antiarrhythmic agents (disopyramide, quinidine, procainamide)
   - Class IB antiarrhythmic agents (lignocaine (lidocaine), mexiletine, aprindine)
   - Class IC antiarrhythmic agents (encaïnide)
   - Class III antiarrhythmic drugs (amiodarone, bretylium, sotalol)
   - Atropine
   - Calcium antagonists (nifedipine)
   - Digoxin, digitoxin
   - Diuretics
   - Vasodilators (prenylamine, lidoflazine, fenoxidil, bepridil)

3. Drugs with predominant action on the central nervous system
   - Amantadine
   - Antidepressants (amitriptyline, doxepine), pimozide
   - Chloral hydrate
   - Lithium
   - Phenothiazines (chlorpromazine, thioridazine), haloperidol

4. Miscellaneous drugs
   - Corticosteroids
   - Gastrointestinal procinetics (cisapride)
   - Histamine antagonists (astemizole, terfenadine), particularly when used with antifungals such as fluconazole, itraconazole, ketoconazole
   - Probucol
   - Tacrolimus

5. Toxins
   - Arsenic
   - Organophosphates

Learning points

- Macrolides, as well as a broad variety of other drugs, may prolong the QT interval, cause torsade de pointes polymorphic ventricular tachycardia, and precipitate sudden death in susceptible individuals.
- If possible, macrolides should therefore be avoided in patients who already receive drugs with a propensity to prolong the QT interval, such as amiodarone and histamine antagonists.

Genetics and molecular pathogenesis of congenital long QT syndrome and at least six forms of the disorder have been attributed to mutations in cardiac ion channels. In the patient reported here, an acquired cause of QT prolongation was suspected since QT intervals had been normal on admission. Electrolyte disturbances such as hypokalaemia or hypomagnesaemia, and drug effects are among the most frequent causes of acquired QT prolongation. Rarely, central nervous system disease or cardiac disorders such as myocardial infarction alone account for prolongation of the QT interval. Our patient had normal serum electrolytes and there were no signs and symptoms nor laboratory evidence of ongoing cardiac ischaemia.

Prolongation of the QT interval has been reported as a side effect of numerous drugs (see box 1). The patient reported here received a total of three drugs with a potential to affect cardiac repolarisation. Before admission he had been on digoxin and amiodarone after several episodes of atrial fibrillation. Amiodarone has a well documented range of side effects, one of them being prolongation of the QT interval. Digoxin, too, can disturb cardiac repolarisation and prolong the QT interval. In hospital, roxithromycin (erythromycin 9-[O-(2-methoxyethoxy)methyl] oxime), a semi-synthetic macrolide antibiotic, was given for community acquired pneumonia. The propensity of macrolides to prolong the QT interval is well documented and their ability to cause polymorphic tachycardia and cardiac arrest has been described in anecdotal reports. Recently, erythromycin was shown to block I\textsubscript{Kr}, the rapid delayed rectifier channel for potassium. Factors that confer increased vulnerability for erythromycin induced QT prolongation are still awaiting further elucidation, although female sex has been proposed to be a risk factor. Interestingly, macrolides occasionally unmask an inherited long QT syndrome; therefore, genetic vulnerability may also play a part. Macrolides may also prolong the QT interval by interacting with the metabolism of other drugs that affect cardiac repolarisation such as histamine antagonists.

We conclude that our patient had acquired prolongation of the QT interval due to concomitant use of digoxin, amiodarone, and roxithromycin. Marked prolongation of the QT interval is associated with a high risk of polymorphic torsade de pointes ventricular tachycardia, ventricular fibrillation and sudden death, more so in patients with advanced myocardial disease. Macrolides should therefore be used with caution or, better still, avoided in patients who already receive other drugs with a propensity to prolong the QT interval. If macrolides cannot be avoided in these patients, for example in chlamydial infection or legionnaire’s disease, we suggest they are used...
cautiously with close monitoring of the QT interval.


Commentary—QT prolongation due to roxithromycin

Alasdair Malcolm

This case and supporting discussion highlight the circumstances in which drug induced prolongation of the QT interval may occur and they serve as a reminder of the associated risk of the serious complication of polymorphic ventricular tachycardia—also known as torsade de pointes—which can lead to ventricular fibrillation and cardiac arrest. The arrhythmia is a non-sustained wide QRS complex (usually >160 ms in duration) tachycardia which tends to occur in repetitive bursts of 4–20 complexes at fast rates (generally 200–250/min) with characteristic variation in QRS amplitude and axis leading to the impression of a certain lead of the electrocardiogram that the QRS complexes are twisting around the isoelectric baseline. In routine clinical practice, a simple correction is used for the rate dependency of the QT interval (Bazett’s formula of QTc = QT/√R-R, where QTc is the rate corrected QT interval in ms, QT is the measured QT interval in ms, and R-R is the R-R interval in seconds). The formula is simple, but imperfect in the sense that it tends to overestimate QT at fast heart rates and underestimate QT at slow heart rates. The upper limit of normal for QTc can be taken as 430 ms in men and 450 ms in women. QTc prolongation is easier to spot if computer interpreted 12 lead electrocardiograms are available, with their routine printout of QT and QTc intervals. QTc values >500 ms should prompt review of the patient’s drug therapy in the light of the catalogue of potential troubleshooters presented here by Woywodt et al. Any clinical features which might indicate bursts of ventricular tachycardia (features such as dizziness, lightheadedness, syncope, or palpitation) or bursts of polymorphic ventricular tachycardia seen on continuous electrocardiographic monitoring demand immediate measurement of QT and calculation of QTc on the best electrocardiographic tracing possible. The true point of termination of the T wave can be quite difficult to identify, especially at faster heart rates, so in clinically critical situations it should be interpreted liberally.

Once the situation of drug induced prolongation of QTc with torsade de pointes has been recognised, immediate action is required.

1 Stop any drugs which have a propensity to prolong the QT interval.
2 Check serum potassium concentration and, if low, commence intravenous potassium supplementation. Aim for a high normal serum potassium.
3 Transfer the patient to a coronary care/cardiac care/intensive care bed where continuous electrocardiographic monitoring and close observation can be implemented.
4 Consider giving intravenous magnesium sulphate initially 2 g over 10–15 minutes. This is viewed by some as the initial treatment of choice.
5 If episodes of torsade de pointes are continuing, and especially if the bursts of tachycardia are becoming more frequent and/or longer, then place a transvenous endocardial pacing catheter with the tip in the right ventricle, or perhaps in the right atrium if a stable tip position with a satisfactory pacing threshold can be achieved, and proceed to “overdrive pacing”. This is often a highly effective way of suppressing bradycardia dependent arrhythmias such as torsades, and pacing at a rate of 100/min should be sufficient.
6 Isoprenaline by intravenous infusion is an alternative way of increasing heart rate and thereby preventing the onset of the bursts of tachycardia. Its use should be allowed only when there is strong confidence that the arrhythmia is indeed one associated with drug induced QT prolongation, for in other ventricular tachyarrhythmias its effect could be disastrous. Overdrive pacing is generally to be preferred.
(7) Avoid using any class Ia, Ic or III antiarrhythmic drugs, for they can increase the abnormal QT interval and exacerbate the arrhythmia problem.  

(8) If the arrhythmia persists, and especially if the situation is deteriorating despite the aforementioned interventions, then consider intravenous bretylium. It is not a “first line” drug in this situation but, as in ventricular fibrillation that has not resolved with DC countershock and the “first line” drugs, bretylium has occasionally been successful in situations which had seemed hopeless.

The management of polymorphic ventricular tachycardia associated with drug induced prolongation of the QT interval is well within the capabilities of clinical teams experienced in managing the arrhythmias and conduction problems of acute myocardial infarction. It is a matter of carrying the patient through the hours or few days necessary for plasma and tissue concentrations of the QT prolonging drug to decline to subcritical levels. With so many drugs now in use which can cause this problem, it is probable that it will be a situation encountered more and more frequently by the on-call hospital medical staff.