orsades de pointes (TdP) is one of the ventricular tachycardias that is induced by antiarrhythmic drugs and noncardiac drugs such as psychotropic medication, antihistamines and antibiotics.1–3 The macrolide antibiotic erythromycin is a commonly prescribed antibiotic and is known to be associated with QT prolongation and TdP.4–6 We report 2 cases in which clarithromycin, a new macrolide antibiotic, induced TdP.

Case Reports

Case 1
A 78-year-old female was referred to hospital because of a syncopeal attack. She was regularly taking digoxin (0.25 mg/day), nilvadipine (4 mg/day), pravastatin (5 mg/day) and loflazepate ethyl (1 mg/day). In addition to these drugs, she had taken clarithromycin (400 mg/day) and chlorpheniramine (12 mg/day) for a respiratory infection (common cold virus) 1 day before the syncopeal attack. Laboratory investigations at the time of admission showed a white blood cell count of 6,160 cells/mm³, hemoglobin 11.6 g/dl, platelets of 221,000 /µl, sodium 143 mmol/L, potassium 3.3 mmol/L and serum creatinine 0.7 mg/dl. Magnesium was not measured. A 12-lead electrocardiogram (ECG) at the time of admission showed marked QT prolongation (0.52 s) at mean heart rate of 95 beats/min and complete right bundle branch block with atrial fibrillation (Fig 1). The patient was transferred to the medical intensive care unit and her ECG was monitored. One hour later the patient became unconsciousness with the development of TdP (Fig 2). Magnesium sulphate was continuously infused and a temporary pacemaker was inserted for 4 days. The pacing rate was set at 80 beats/min. Echocardiography showed an enlarged left atrium although the left ventricular size and wall motion were essentially normal. A chest radiograph showed slight cardiac enlargement [cardiothoracic ratio (CTR)=54.5%]. Ten days later, she was discharged from hospital. The QT interval at that time was 0.36 s.

Case 2
A 62-year-old male patient with idiopathic interstitial pneumonia and chronic hepatitis C was treated with theophylline (400 mg/day), cloperastine (60 mg/day), clarithromycin (400 mg/day) and zopiclone (10 mg/day). After a short time at home he was rushed to the hospital suffering from convulsions and cyanosis. It was observable from the heart monitor that he was having nonsustained episodes of TdP. An ECG showed normal sinus rhythm (rate, 69 beats/min) with QT interval prolongation (0.56 s) (Fig 3). His serum potassium was 3.9 mmol/L, serum creatinine was 0.8 mg/dl, glutamic-oxaloacetic transaminase was 188 IU, and glutamic pyruvic transaminase was 208 IU. Magnesium was not measured. Clarithromycin was discontinued. He was given 2 g magnesium sulphate intravenously and a temporary pacemaker was inserted. A chest radiograph revealed curvilinear strands along with some linear

Acknowledgment

T
orsades de pointes (TdP) is one of the ventricular tachycardias that is induced by antiarrhythmic drugs and noncardiac drugs such as psychotropic medication, antihistamines and antibiotics.1–3 The macrolide antibiotic erythromycin is a commonly prescribed antibiotic and is known to be associated with QT prolongation and TdP.4–6 We report 2 cases in which clarithromycin, a new macrolide antibiotic, induced TdP.

Case Reports

Case 1
A 78-year-old female was referred to hospital because of a syncopeal attack. She was regularly taking digoxin (0.25 mg/day), nilvadipine (4 mg/day), pravastatin (5 mg/day) and loflazepate ethyl (1 mg/day). In addition to these drugs, she had taken clarithromycin (400 mg/day) and chlorpheniramine (12 mg/day) for a respiratory infection (common cold virus) 1 day before the syncopeal attack. Laboratory investigations at the time of admission showed a white blood cell count of 6,160 cells/mm³, hemoglobin 11.6 g/dl, platelets of 221,000 /µl, sodium 143 mmol/L, potassium 3.3 mmol/L and serum creatinine 0.7 mg/dl. Magnesium was not measured. A 12-lead electrocardiogram (ECG) at the time of admission showed marked QT prolongation (0.52 s) at mean heart rate of 95 beats/min and complete right bundle branch block with atrial fibrillation (Fig 1). The patient was transferred to the medical intensive care unit and her ECG was monitored. One hour later the patient became unconsciousness with the development of TdP (Fig 2). Magnesium sulphate was continuously infused and a temporary pacemaker was inserted for 4 days. The pacing rate was set at 80 beats/min. Echocardiography showed an enlarged left atrium although the left ventricular size and wall motion were essentially normal. A chest radiograph showed slight cardiac enlargement [cardiothoracic ratio (CTR)=54.5%]. Ten days later, she was discharged from hospital. The QT interval at that time was 0.36 s.

Case 2
A 62-year-old male patient with idiopathic interstitial pneumonia and chronic hepatitis C was treated with theophylline (400 mg/day), cloperastine (60 mg/day), clarithromycin (400 mg/day) and zopiclone (10 mg/day). After a short time at home he was rushed to the hospital suffering from convulsions and cyanosis. It was observable from the heart monitor that he was having nonsustained episodes of TdP. An ECG showed normal sinus rhythm (rate, 69 beats/min) with QT interval prolongation (0.56 s) (Fig 3). His serum potassium was 3.9 mmol/L, serum creatinine was 0.8 mg/dl, glutamic-oxaloacetic transaminase was 188 IU, and glutamic pyruvic transaminase was 208 IU. Magnesium was not measured. Clarithromycin was discontinued. He was given 2 g magnesium sulphate intravenously and a temporary pacemaker was inserted. A chest radiograph revealed curvilinear strands along with some linear
and ring-shaped opacities in all lung fields. No cardiac enlargement was observed [CTR = 48%]. Echocardiogram was normal. He was discharged without arrhythmia. An ECG recorded 40 days after the convulsion attack revealed a shortened QT interval of 0.48 s (heart rate was 56 beats/min).

Discussion

Macrolide antibiotics are commonly prescribed for upper respiratory infections as well as for chronic respiratory disease. TdP is a multiform ventricular tachycardia associated with prolonged QT interval and is often induced by antiarrhythmic drugs as well as noncardiac drugs. Erythromycin-induced TdP is well-known and its mechanism has already been reported in detail. Rubart et al reported that erythromycin prolongs the action potential duration by blocking of the potassium channels and promotes the development of early afterdepolarization.  

Clarithromycin is one of the macrolide antibiotics. Although erythromycin has been reported to cause QT prolongation mostly when used with other drugs associated with TdP, Granberry et al reported erythromycin monotherapy associated with TdP. To our knowledge, there is at present only 1 case report in which clarithromycin induced TdP in chronic renal failure patients receiving long-term cisapride therapy. The latter drug itself already known to induce TdP. They suggested that the inhibition of cytochrome P-450 3A4 by clarithromycin affects cisapride metabolism and results in increased serum cisapride levels.

We have reported here 2 cases of clarithromycin associated with TdP in the absence of other drugs known to produce QT prolongation. Although the precise mechanism of clarithromycin-induced TdP is unknown, it may be similar to erythromycin-induced TdP, as described earlier. Overt evidence of organic heart disease was not disclosed by echocardiography, and the left ventricular systolic function was normal in both cases. In case 1, although we diagnosed atrial fibrillation only, latent organic heart disease might exist because the left atrium was enlarged. Hypokalemia, which is known to be related to QT prolongation, was also found in case 1. In case 2, other factors, such as age and the pulmonary disease associated with the hypoxemia, may have played a role in the QT prolongation and TdP.

In conclusion, we presented 2 elderly patients with prolonged QT interval and TdP induced by clarithromycin. Although the incidence of TdP induced by clarithromycin is rare, we should be cautious when prescribing it and ECGs are necessary in the follow-up of patients, particularly the elderly, receiving this drug.

References


Fig 3. Case 2. Electrocardiograms recorded on re-admission (left) and at discharge (right).