Torsade de pointes in a patient with bronchopenumonia and atrial fibrillation treated with clarithromycin

Lihua Fang¹, Chung-Jen Huang²*, Hwang-Daw Hua³ and Chung-Hsin Huang⁴

¹Department of Pharmacy, Koo Foundation Sun Yat-Sen Cancer Center, Taipei, Taiwan.
²Division of Pulmonary Medicine and Intensive Care Medicine, Koo Foundation Sun Yat-Sen Cancer Center, Taipei, Taiwan.
³Division of Cardiology, Koo Foundation Sun Yat-Sen Cancer Center, Taipei, Taiwan.
⁴Department of Anesthesiology, Mackay Memorial Hospital, Hsinchu, Taiwan.

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Clarithromycin is a macrolide antibiotic widely used in pulmonary infection and Helicobacter pylori eradication. QT prolongation on an electrocardiogram with torsade de pointes is an uncommon fatal side effect. We report a patient with atrial fibrillation and congestive heart failure who develops torsade de pointes after clarithromycin, tamoxifen, amoxicillin/clavulanate, digoxin and verapamil use, and discuss the pharmacological mechanism and prevention.

Key words: Torsade de pointes, clarithromycin, atrial fibrillation, QT interval.

INTRODUCTION

Torsade de pointes is a specific variety of ventricular tachycardia that exhibits distinct characteristics on the electrocardiogram. It usually results from long QT syndrome which can either be inherited, or drug induced. Clarithromycin (6-0-methylerythromycin) is a semi-synthetic macrolide antibiotic. It is commonly applied for community acquired pneumonia and Helicobacter pylori eradication during peptic ulcer, but side effects such as diarrhea, nausea, vomiting, abdominal pain, headache, pseudomembranous colitis and abnormal sense of taste have been previously reported. Torsade de pointes is an uncommon fatal complication of clarithromycin. This is a case of torsade de pointes probably induced by clarithromycin in a patient with atrial fibrillation and congestive heart failure.

Case report

A 53-year-old Taiwanese woman with normal heart function was diagnosed with advanced breast cancer in 2001. She received preoperative chemotherapy consisting of 3 cycles of epirubicin, cyclophosphamide, and fluorouracil and underwent modified radical mastectomy as initial treatment. Postoperative adjuvant chemotherapy consisting of 3 cycles of sequential doxorubicin, paclitaxel, and cyclophosphamide were administered between December 2001 and July 2002. The cumulative dose of doxorubicin was 375 mg/m². Then she received tamoxifen as adjuvant hormone therapy. She was admitted to our hospital in April 2005 because of bronchopneumonia. Her electrocardiogram showed new onset of atrial fibrillation with torsade de pointes after clarithromycin, tamoxifen, amoxicillin/clavulanate, digoxin and verapamil use, and discuss the pharmacological mechanism and prevention.

Key words: Torsade de pointes, clarithromycin, atrial fibrillation, QT interval.
DISCUSSION

Myocardial repolarization is primarily mediated by the efflux of potassium ions into the cytoplasm. Drugs that block the rapid rectifier potassium current prolong the QT interval (Gupta et al., 2007). Torsades de pointes may occur after one or more premature ventricular complexes and a compensatory pause. The subsequent sinus beat usually has a long QT interval that precipitates torsades de pointes. Many drugs prolong the QT interval such as class IA and class III antiarrhythmics, methadone, lithium, tricyclic antidepressants, phenothiazines, and many antibiotics. (Gupta et al., 2007) Erythromycin was the first macrolide antibiotic available and was documented to cause QT prolongation and torsade de pointes (Gitter et al., 1994) (Schoenenberger et al., 1990). It has been shown in vitro that erythromycin can prolong the action potential by blocking the potassium currents (Nattel et al., 1990). Clarithromycin has a similar chemical structure to erythromycin, and they share similar electrophysiological properties and arrhythmogenic potential. Clarithromycin induced torsade de pointes was first reported in 1998 (Lee et al., 1998). Because the use of clarithromycin is increasing in treatment of pulmonary infections and H. pylori eradication, some clarithromycin related QT prolongation and torsades de pointes were reported and reviewed thereafter (Piquette et al., 1999; Shaffer et al., 2002; Curtis et al., 2003). Although the incidence of ventricular arrhythmias or cardiac arrest was less than 0.1%, the drug safety of clarithromycin is important and requires more attention.

So far no documented data has indicated that the monitoring of the QT interval can decrease the incidence of drug induced torsade de pointes. The monitoring of the QT interval was not practical in an outpatient setting. In our institute, we did not routinely monitor the QT interval when a patient was receiving medication known to be associated with torsade de pointes. In this patient, the QT interval was monitored because of atrial fibrillation and congestive heart failure. Her QT interval was normal before the torsade de pointes occurred. This implied drug induced torsade de pointes may occur in patients with a previous normal QT interval.

The patient has received multiple chemotherapy for breast cancer. The cumulative dose of doxorubicin was 375 mg/m². In a previous study, the possibility of doxorubicin induced congestive heart failure was low at the cumulative doses of doxorubicin below 550 mg/m². (Von et al., 1979). It was shown that the incidence of congestive heart failure from doxorubicin combined with paclitaxel is increased when the cumulative dose of doxorubicin was over 380 mg/m² (Gianni et al., 2001). It was also reported that the combination of doxorubicin and cyclophosphamide may decrease the left ventricular function (Perez et al., 2004). The underlying cause of congestive heart failure may be related to the multiple chemotherapy and was aggravated by the pneumonia episode. It has been reported that most patients with drug-induced torsade de pointes have easily identifiable risk factors (Zelter et al., 2003; Pedersen et al., 2007; Simkó et al., 2008). In patients with drug induced torsade de pointes, more than 90% of the patients had one risk factor such as female gender, advanced age, structural heart disease, genetic predisposition, electrolyte abnormalities, or the corrected QT interval over 450 milliseconds on baseline electrocardiogram. It is likely for a combination of risk factors work in synergy in the individual patient to produce torsade de pointes (Roden et al., 2002). The risk factors of our patient are female gender, congestive heart failure and corrected QT interval of 477 milliseconds on admission. In patients with complicated underlying disease, the use of clarithromycin should be proceeded with care. Measuring of the QT interval is difficult in atrial fibrillation because the QT interval varies from beat to beat. It was suggested to measure more than 10 continuous QRS intervals to calculate the average corrected QT interval in patients with atrial fibrillation (Al-Khatib et al., 2003). QT interval over 500 milliseconds is associated with increased risk of torsade de pointes (Priori et al., 2003).

In summary, clarithromycin induced torsade de pointes is a rare but serious complication. The efficacy of monitoring the QT interval is still controversial in patients receiving clarithromycin. For patients with a QT interval longer than 500 milliseconds or a pre-existing heart disease, clarithromycin should be substituted by other antibiotics to reduce the incidence of torsade de pointes. A normal QT interval cannot indicate the absence of drug induced torsade de pointes.

REFERENCES

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