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Full Length Research Paper

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

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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, amoxillin/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 syn-drome 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 clarith-romycin in a patient with atrial fibrillation and congestive heart failure.

Case report

A 53-year-old Taiwanese woman with normal heart func-tion 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 consis-ting of 3 cycles of sequential doxorubicin, paclitaxel, and cyclophosphamide were administered between Decem-ber 2001 and July 2002. The cumulative dose of doxoru-bicin was 375 mg/m^2. 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 rapid ventricular rate and the corrected QT interval was found to be 477 millisecond. The QT interval was measured from QRS complex onset to T wave termina-tion; the corrected QT interval was the longest QT inter-val divided by the square root of the RR interval. (Gupta et al., 2007) The echocardiography showed the ejection fraction was 34% with dilated left atria and ventricle, which was consistent with congestive heart failure. The patient had no risk factors of congestive heart failure such as ischemic heart disease, previous myocardial infarction, long-standing history of hypertension, valvular heart disease, or myocardial heart disease. The cause of her congestive heart disease may be chemotherapy induced cardiac toxicity and recent bronchopneumonia. Empiric antibiotics consisting of intravenous amoxycillin/ clavulanate and oral clarithromycin (250 mg twice a day) were prescribed. Digoxin, 0.25 mg (oral; once a day) and verapamil, 120 mg (oral; once a day) were given for heart rate control. Her heart rate was between 70-100 beats/

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min under the medication. Tamoxifen was discontinued on admission. After 7 days of treatment, her pneumonia was improved and the corrected QT interval on the electrocardiogram was 435 millisecond at that time. On the 8^{th} day she was found to be unresponsive and pulseless on the ward suddenly, and her electrocardiogram showed torsades de pointes. Electric defibrillation was performed immediately after which sin-us rhythm was restored. Her plasma sodium, potassium, magnesium and calcium were within normal range. The patient had no family history of sudden death and no known history of prolong QT interval. Her renal and liver function was normal. All the medications including verapamil, digoxin, and antibiotics were discontinued, and no torsade de pointes re-occurred thereafter, but the corrected QT interval went up to be 510 millisecond. The patient went home and re-mained well at 6 months follow-up. Her electrocardiogram still displayed atrial fibrillation with ventricular rate of 78 beats /min and average corrected QT interval of 473 millisecond during regular follow up.

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). Torsade 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 torsade 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 (Gitler 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., 002; 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/m^2. In a previous study, the possibility of doxorubicin induced congestive heart failure was low at the cumulative doses of doxorubicin below 550 mg/ m^2 .(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/m^2 (Gianni et al., 2001). It was also reported that the combination of doxorubicin and cyclophophamide 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 millisecond 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 millisecond 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 millisecond 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 millisecond 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

Al-Khatib SM, LaPointe NM, Kramer JM, Califf RM (2003). What clinicians should know about the QT interval. JAMA 289: 2120-2127.

Curtis LH, Ostbye T, Sendersky V, Hutchison S, Allen LaPointe NM, Al-Khatib SM, Usdin Yasuda S, Dans PE, Wright A, Califf RM, Woosley RL, Schulman KA (2003). Prescription of QT prolonging drugs in a cohort of about 5 million outpatients. Am. J. Med.114: 135-141.

Gianni L, Dombernowsky P, Sledge G, Martin M, Amadori D, Arbuck SG, Ravdin P, Brown M, Messina M, Tuck D, Weil C, Winograd B (2001). Cardiac function following combination therapy with paclitaxel and doxorubicin: an analysis of 657 women with advanced breast cancer. Ann. Oncol. 12: 1067-1073.

Gitler B, Berger LS, Buffa SD (1994). Torsade de pointes induced byerythromycin. Chest. 105: 368-372.

Gupta A, Lawrence AT, Krishnan K, Kavinsky CJ, Trohman RG (2007). Current concepts in the mechanisms and management of drug-induced QT prologation and torsade de pointes. Am. Heart J. 153: 891-899.

Lee KL, Jim MH, Tang SC, Tai YT (1998). QT prolongation and Torsade de pointes association with clarithromycin. Am. J. Med. 104: 395-396.

Nattel S, Ranger S, Talajic M, Lemery R, Roy D (1990). Erythromycin-induced long QT syndrome: concordance with quinidine and underlying cellular electrophysiological mechanism. Am. J. Med. 89: 235-238.

Pedersen HS, Elming H, Seibaek M, Burchardt H, Brendorp B, Torp-Pedersen C, Køber L (2007). Risk factors and predictors of torsade de pointes ventricular tachycardia in patients with left ventricular systolic dysfunctionreceiving dofetilide. Am. J. Cardiol. 100: 876-880.

Perez EA, Suman VJ, Davidson NE, Kaufman PA, Martino S, Dakhil SR, Ingle JN, Rodeheffer RJ, Gersh BJ, Jaffe AS (2004). Effect of Doxorubicin plus cyclophosphamide on left ventricular ejection fraction in patients with breast cancer in the north central cancer treatment group N9831 intergroup adjuvant trial. J. Clin. Oncol. 22: 3700-3704.

Piquette RK (1999). Torsade de pointes induced by cisapride/clarithromycin interaction. Ann. Pharmacother. 33: 22-26.

Priori SG, Schwartz PJ, Napolitano C, Bloise R, Ronchetti E, Grillo M, Vicentini A, Spazzolini C, Nastoli J, Bottelli G, Folli R, Cappelletti D (2003). Risk stratification in the long-QT syndrome. N. Engl. J. Med. 348: 1866-1874.

Roden DM, Balser JR, George AL Jr., Anderson ME (2002). Cardiac ion channels. Annu. Rev. Physiol. 64:431-475.

Schoenenberger RA, Haefeli WE, Weiss P, Ritz R (1990). Association of intravenous erythromycin and potentially fatal ventricular tachycardia with QT prolongation (torsade de pointes). BMJ 300: 1375-1376.

Shaffer D, Singer S, Korvick J, Honig P (2002). Concomitant risk factors in reports of torsade de pointes associated with macrolide use: Review of the United States food and drug administration adverse event system. Clin. Infect. Dis. 35: 197-200.

Simkó J, Csilek A, Karászi J, Lorincz I (2008). Proarrhythmic potential ofantimicrobial agents. Infect. 36(3): 194-206.

Von Hoff DD, Layard MW, Basa P, Davis HL Jr., Von Hoff AL, Rozencweig M, Muggia FM (1979). Risk factors for doxorubicin-induced congestive heart failure. Ann. Intern. Med. 91: 710-717.

Zelter D, Justo D, Halkin A, Prokhorov V, Heller K, Viskin S (2003). Torsade de pointes due to noncardiac drugs: most patients have easily identifiable risk factors. Med. (Baltimore). 82: 282-290.