Torsades de pointes induced by metoclopramide injection

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ABSTRACT

Torsades de pointes is one of polymorphic ventricular tachycardia disorder, caused of prolongation of QT interval more than 500 ms. This is a report about a 71-year-old male patient with metoclopramide induced torsades de pointes. Administration of metoclopramide in normal dose intravenously can cause prolongation of QT interval that may cause torsades de pointes by blocking on the 5-HT4 receptor. Management of torsades de pointes due to medication are by defibrillation and discontinuation of the drug which are the triggering factor of the torsades de pointes.

Keywords: torsades de pointes, drug-induced arrhythmia, drug reaction, metoclopramide


INTRODUCTION

Torsades de pointes (Tdp) is a polymorphic ventricular tachycardia disorder, in which the ventricle contracts irregularly more than 200 to 250 beats per minute, with the varying QRS axis and appeared to form a twisting of point.1,2 The exact prevalence of Tdp is not yet known but estimated around 5% of 300,000 cases of sudden death in the USA caused by Tdp. This syndrome is more common in women than in men with ratio about 2–3:1.3

The mechanism of Tdp is associated with prolongation of QT interval more than 500 ms. QT interval may be provoked, for example, by electrolyte abnormalities, medication that lead to ion flow disturbances in the heart and result in an increase of cardiac muscle potential duration in the early after depolarization phase. As the consequence, cardiac repolarization interval becomes long, followed by the oscillation of the cardiac muscle membrane. Cardiac muscle is provoked, and finally, the heart will contract irregularly.4,5

One of the cause of prolonged QT intervals is medication such as amiodarone, amitriptyline, azithromycin, chloroquine, loperamide, and metoclopramide, among others. Metoclopramide is a drug to prevent and treat vomiting in patient with gastrointestinal disease. Several literatures show that some patients receiving metoclopramide medication have cardiac arrest, bradycardia, total AV block, acute hypotension, supraventricular tachycardia, prolonged QT intervals, Torsade de Pointes, ST depression, and heart failure. Some complications are reported with normal dose of intravenous administration.6

CASE ILLUSTRATION

A 71 years old man, a retired government employee, was consulted by the Internal Medicine Department with chief complaint of palpitation with cold sweating since 1 day before admission. He also felt weak, and had had diarrhea since 3 days before.
CASE ILLUSTRATION

For the diarrhea complaint, the fecal matter was yellow without sludge and mucus, and the patient defecated 4-5 times per day. He also complained about pain all over the abdomen, fever, nausea, vomiting, and few urine.

He had no complaint of chest pain. But 2 years ago, patient had experienced chest pain but the pain is reduced after placing the coronary stent. He had hypertension, dyslipidemia, and diabetes as coronary heart disease risk factors. Regularly he took clopidogrel, simvastatin, candesartan, amlodipine, metformin. He also took isosorbide dinitrate occasionally for chest pain reliever. He had history of smoking and stopped for 1 year, and there was no history of alcohol consumption.

Physical examination showed irregular 70 beats per minute pulse and fever (38.2°C). Cardiac examination revealed enlarged heart and irregular heart rate was 164 beats per minute with neiter murmur nor gallop. Abdominal examination showed increase of bowel sound.

Laboratory findings were leukocytosis (18000/µL), increased creatinine (2.6 mg/dL), normal potassium level (1.9 mEq/L), normal magnesium level (1.9 mEq/L), high blood glucose level (210 mg/dL), normal troponin-T (0.01 ng/mL), normal INR (1.8).

Electrocardiogram showed atrial fibrillation with irregular heart beats 150 per minute, pathologic q wave at lead III, aVF, poor r wave progression in V1-V4, left ventricular hypertrophy (LVH) with strain in lateral leads (figure 1).

Based on the history, physical examination and some workups, he was diagnosed with rapid ventricular response by atrial fibrillation, congestive heart failure with functional class II caused by coronary artery disease or hypertensive heart disease, coronary artery disease post percutaneous transluminal coronary angioplasty (PTCA), acute gastroenteritis with dehidration, acute kidney injury, and type II diabetes mellitus.

This patient was treated with bed rest, administration of normosaline infusion, digoxin injection 0.25 mg IV, warfarin 4 mg od, simvastatin 20mg od, candesartan 8 mg od, ceftriaxone injection 1 gr bid, lansoprazole 30 mg od, insulin aspart 4 IU tid, and loperamide 2 mg tid.

On the second day of treatment, no complaint of palpitation. Electrocardiogram showed atrial fibrillation with irregular heart beats 60 per minute, pathologic q wave at lead III, aVF, poor r wave progression in V1-V4, left ventricular hypertrophy (LVH) with strain in lateral leads (figure 2).

On the fourth day of treatment, he complained of nausea, vomiting four times in 12 hours. His vital signs are within normal limit. Then he was given metoclopramide 10 mg injection via central venous line. After 5 minutes of administration the patient had seizure with ventricular tachycardia without pulse on ECG monitor. Then we performed resuscitation, defibrillated with unsynchronized 200 joule. The post defibrillation rhythm was sinus rythm with prolonged QTc and multiple premature ventricular contractions (figure 3). After some while, the patient had seizure again and there was “R on T” on monitor and torsades de pointes rhythm without pulse (figure 4). We performed resuscitation and defibrillation again. The patient was gived magnesium sulfate (MgSO₄) 20% 5 cc intravenously,
then the ECG became sinus bradycardia rhythm with pulse 50 beats per minute (figure 5). Metoclopramide and loperamide were stopped, candesartan was postponed.

On the fifth day of treatment, we performed coronary angiography on the patient and found that left main coronary artery appeared normal, patent stent on mid segment of left anterior descending artery and proximal segment of diagonal-1, normal left circumflex artery and normal right coronary artery (figure 6). Echocardiography showed left atrium, right atrium, right ventricle chamber dilatation, spontaneous echo contrast in left atrium, normal systolic left ventricular function with ejection fraction 67%, decreased right ventricular systolic function with TAPSE 1.24 cm, hypokinetic left ventricle segmental wall.

On the sixth day of admission, patient had no complaint and was sent home.

DISCUSSION

Torsades de pointes rhythms appear more irregular than ventricular fibrillation. A rapid TdP episode characterized by a long duration beginning with rapid heartbeat and often end in ventricular fibrillation. In most cases, TdP is preceded by long R-R intervals as a basic rhythm, followed by short extrasystolic interval with premature depolarization on T wave. This pattern is not a typical sign of TdP. In some cases, TdP is preceded by ventricular tachycardia and fibrillation. Torsades de pointes rhythm may return to normal (sinus rhythm) or may end with ventricular fibrillation and sinus arrest with slow ventricular escape rhythm.3,4

Torsade de Pointes generally occur in conditions that associated with prolonged QT interval. Risk factors for TdP are increased QTc interval and in some conditions including hypokalemia, hypophosphatemia, hypomagnesemia, ventricular disturbances, severe bradycardia, 3rd degree AV block, T wave alternans, or R on T phenomenon. The predisposing factors of TdP are the use of anti-arrhythmia drugs, medication that prolong the QT interval, metabolic disorder or acute phase of myocardial infarction.3,4 In this patient, before TdP happened, there was a prolongation of QTc interval for 0.53 sec and there was R on T phenomenon that continued into TdP.

QT prolongation is a condition where the cardiac repolarization phases becomes slow, resulting in the occurrence of a harmful polymorphic ventricular TdP. The basic mechanism of prolonged QT interval is due to inhibition of potassium outflow, with the consequence of elongated repolarization that cause...
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re-entry. This K⁺ canal is encoded by human ether-a-go-go-related gene (hERG). Inhibition of the potassium hERG flow by class III anti-arhythmia drugs can cause an excessive potential action excursion due to Ca²⁺/Na⁺ re-entry can cause QT interval lengthening.³

Clinical features of TdP are palpitation, dizziness, fainting, and sudden death. The physical examination on TdP may be a rapid heartbeat, normal or low blood pressure, and loss of consciousness that can be preceded by bradycardia or premature ventricular contraction, or other findings based on TdP.¹,³

The diagnosis of TdP at the patient is made based on ECG images of polymorphic type ventricular tachycardia with variable QRS complex on the axis or morphology. Previous ECG images showed a R on T phenomenon that initiates TdP, which then results in ventricular fibrillation. When QT interval measurement was taken before TdP, measurement using Bazet formula and found the corrected QT interval 530 milisecond that means the prolonged QT interval is more than 430 milisecond in male. QT interval more than 500 millisecond is associated with increased risk of TdP. The etiology of TdP in this patient consist of many factors such as underlying heart disease, as well as use of loperamide and metoclopramide.⁷,⁹

Loperamide is an opioid receptor agonist and acts on opioid receptor in the myenteric plexus of large intestine, thus decreasing bowel muscle tone. The mechanism of prolonged QT interval due to loperamide is not yet certainly known, but there are some literature that mention loperamide can inhibit receptor potassium hERG. Loperamide has the same structure as methadone which is a potent hERG inhibitor, has three phenyl ring molecules that facilitate blocking of hERG, thus explain how loperamide is also associated with TdP.¹⁰ In some literature and case reports explained that loperamide can cause a prolonged QT interval in high doses, in the case report obtained the dose that can cause elongation of QT interval is 25-200 mg, while the recommended maximal dose is 16 mg per day, overdose of loperamide usually occur in opioid user.¹¹,¹² This patient use a dose of 2 mg tid, so when compared to the literature, loperamide was less likely to be the cause TdP in this patient.

Metoclopramide is 4-amino-5-chloro-N-[2-(diethylamino)ethyl]-2-methoxy benzenecarboximide acid which is a class of dopaminergic antagonist with a structure similar to that procainamide. Metoclopramide is a drug to prevent and treat vomiting and also esophageal reflux disease, gastroparesis dyspepsia, and another gastrointestinal disease. Some literatures showed that some patients receiving metoclopramide treatment had cardiac arrest, bradycardia, total AV block, acute hypotension, supraventricular tachycardia, prolonged QT interval, Torsade de Pointes, ST depression, and heart failure. The incidence of complication was reported with intravenous administration of normal 10 mg.⁶ Patient in this report got a Torsade de Pointes after 10 mg metoclopramide intravenous administration that before TdP occur preceed byelongation of QTc interval 0.53 second after ventricular tachycardia that performed a DC shock.

The effects of metoclopramide on cardiovascular system were first reported in 1974. Metoclopramide is a benzamide derivate that has side effects in 10-20% patients. The effect of using metoclopramide in patients with heart failure has a different mechanism by inhibiting dopaminergic receptor, thereby increasing plasma aldosterone levels and retention of sodium occurs. In some literature it may also causing a supraventricular tachycardia, AV blocks, bradycardia, heart failure, hypotension, cardiac arrest, torsades de pointes, prolongation of QT interval and ST depression. The mechanism of TdP due to metoclopramide is remain uncertain, but is likely because of a direct block on presynaptic autoreceptor and cathecholamine release that inhibit cholinergic neurotransmission and might cause blocking of 5-HT3 receptor and 5-HT4 agonist receptor. 5-HT4 receptor is also found in the heart and blood vessel that have a positive chronotropic effect and also cause tachycardia. The structure of metoclopramide similar to cisapride. Cisapride can cause tachycardia and supraventricular tachycardia by stimulating 5-HT4 receptor and can also cause TdP. This effect is increased especially in patient with medication that also inhibit CYP3A4.⁶,¹³

Treatment for TdP in this case are defibrillation, stopping and correction of precipitating factors.¹ In this reported case, we stopped the metoclopramide as it was suspected as TdP trigger.

CONCLUSION

This report describes a case of a patient with complaint of acute gastroentritis and treated with metoclopramide. With normal dose of metoclopramide and comorbidity of heart failure, pulseless torsades de pointes was induced. The present case demonstrates drug induced arrhythmia may lead to a life-threatening incident. Therefore, clinicians should closely monitor the electrocardiogram (ECG) when QTc-prolonging drug are given to patients.
REFERENCES


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