Abstract:
Drug-induced torsades de pointes (TdP) is a rare but potentially fatal adverse effect of commonly prescribed medications including cardiac and noncardiac drugs. Importantly, many drugs have been reported to cause the characteristic Brugada syndrome-linked electrocardiography (ECG) abnormalities and/or (fatal) ventricular tachyarrhythmias. Chlorpheniramine and propranolol have the arrhythmogenic effects reported previously. A review of literature revealed a large number of case reports of chlorpheniramine or propranolol use resulting in QTc prolongation, TdP, or both. However, we wish to report the case of a patient who was treated with a combination of chlorpheniramine and propranolol, whose ECG showed no QT prolongation but who suffered from cardiac arrest due to TdP.

Key words:
Chlorpheniramine, drug-induced torsades de pointes, propranolol

Acquired torsades de pointes (TdP) is a fatal arrhythmia that usually results from drug therapy or electrolyte abnormalities.[1] Current use of any noncardiac QT prolonging drug was associated with a significantly increased risk of sudden cardiac death (adjusted odds ratio [OR] 2.7), and the highest risk was associated with antipsychotic drugs (adjusted OR 5.0). In more than 90% cases of acquired TdPs, there is QT prolongation but TdP might occur without QT prolongation, this is true particularly for ischemic acquired TdPs.[2] We wish to present a rare case of acquired TdP without QT prolongation that was triggered by the concomitant use of chlorpheniramine and propranolol.

Case Report

A 35-year-old man was hospitalized for acute chest pain and palpitation at rest with a presumed diagnosis of unstable angina. He also described an episode of syncope. He was prescribed chlorpheniramine 4 mg a couple of days ago for symptomatic treatment of upper respiratory tract infection, and he was also on propranolol 20 mg treatment for essential tremor and anxiety disorder for many years. He was used to take propranolol daily. His complaints appeared 1 h after intake of the second dosage of chlorpheniramine together with propranolol. He had no prior history of cardiac arrhythmias, valvular or congenital heart disease, and sudden cardiac death in family history. He smoked regularly up to 20 cigarettes a day. He denied the usage of legal or illegal other medications such as antidepressants and cocaine. Physical examination revealed irregular pulse, low blood pressure of 90/60 mmHg, and altered cloudy consciousness. He had no biochemical abnormality; magnesium and potassium level was in normal range. Electrocardiography (ECG) showed ST-segment depression in inferior leads and isolated ST elevation in leads D1-aVL [Figure 1]. Echocardiography showed normal systolic functions with no segmental wall motion abnormalities. The patient was given 300 mg of acetylsalicylic acid and underwent emergency coronary angiography that revealed normal coronary arteries. Whenever ischemic changes were observed in admission ECG, anti-ischemic therapy was not admitted to the patient due to the result of completely normal
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Since the patient had no structural heart disease, no cardiac rhythm disturbance, no family history of sudden cardiac death, no legal or illegal any other medications, or no substance abuse; we assumed it to be an adverse drug reaction (ADR).

In patients who had cardiac arrest at young age and who does not have organic heart disease, genetic abnormalities of heart’s electrical system and drugs that might cause long QT should be kept in mind. Drug-induced TdP that ends with sudden death is a rare unwanted event that heightens many people concerns regarding drug safety and exerts a profound impact on the development of new drugs. The estimation of the frequency of drug-induced TdP is difficult because many cases have not been reported in the literature, and some cases may not be suspected if the patient had another good reason for sudden death, such as heart failure.[1] The awareness of drug-induced TdP in the last few years has resulted in an increase in the number of spontaneous reports. We have seen polymorphic VT without QT prolongation in our patient. Even though it is rare, TdP might be seen in patients with normal or short QT intervals.[2] Although normal QT interval usually

coronaries. After all the patient was followed by telemetry at coronary care unit. Control ECG showed ventricular bigeminy and R on T phenomenon. On the 2nd day of admission, the patient had polymorphic ventricular tachycardia (VT) attack which degenerated to ventricular fibrillation, immediately patient was defibrillated and sinus rhythm was restored successfully [Figure 2]. After defibrillation, the patient continued to have frequent premature ventricular beats and couplets on the monitor. On the 3rd day of his admission, an upper rib ECG was performed and showed a pattern of right bundle branch block with ST-segment elevation in leads V3. The present findings were thought to be compatible with Type 3 Brugada syndrome [Figure 3]. An ajmaline challenge test[8] was then performed. Although the frequency of ventricular extrasystoles and couplets was increased during the test, no coved-type ECG pattern appeared in the right precordial leads [Figure 4]. Therefore, the diagnosis of Brugada syndrome was abandoned. Electrophysiological study was proposed, but the patient refused the test. Because the patient survived a sudden unexplained cardiac arrest, it was decided to implant an implantable cardioverter defibrillator for secondary prevention. The patient recovered and had no further complaints after implantation and he was discharged.

Discussion

Figure 1: ST Depression in inferior leads and isolated ST elevation In D1-aVL

Figure 2: Follow-up electrocardiography showing polymorphic ventricular tachycardia, ventricular fibrillation, and sinus rhythm
detected in ischemic VT, in our patient coronary angiography was completely normal.

The second generation antihistaminic drugs are known to prolong the QTc interval and lead to cardiac arrhythmias; however, publications about chlorpheniramine\(^5\) and diphenhydramine that they caused QT prolongation and TdP are limited.\(^4\) And also propranolol a nonselective beta-adrenergic receptor blocking agent which was used frequently for cardiac arrhythmias is known to cause human ether-a-go-go-related gene (hERG) blockade and QT prolongation.\(^5\)

The unintended block of hERG channels by drugs may prolong the cardiac action potential duration and induce arrhythmia, some drugs not only block hERG channels but also enhance channel activation after the application of a depolarizing voltage step by named of facilitation. Compounds such as drugs that show only weak facilitation could thus be associated with drug-induced arrhythmia and the arrhythmia inducing side effects of compounds should be assessed in terms of both hERG channel facilitation and block.\(^6\)

In an experimental study on frog’s *Xenopus* oocytes which has been performed by Yamakawa *et al.*, the property of drugs that induce hERG channel facilitation was extracted. In this study, for chlorpheniramine and propranolol, block constructive effects were higher than facilitation effects.\(^5\) It is difficult to interpret these findings in human, but in theory, we conclude that our patient’s susceptibility to arrhythmias resulted from strong hERG blockade with the potentiation of each drug. Our patient had ingested propranolol and chlorpheniramine concomitantly in the morning of the event. Seeing that both drugs are metabolized by the cytochrome p450 pathway, drug-drug interaction is not favored on the line, and no other satisfactory reason was found to explain. Since both drugs are metabolized by the cytochrome p450 pathway, the possibility of drug-drug interaction cannot be excluded. The Naranjo ADR probability rating scale evaluate the probability of an event being related with a medication,\(^9\) and in this case, it has indicated a probable association, with a score of 7. If we look at the World Health Organization-Uppsala Monitoring Centre Causality Categories, it would be logical to use the possible term for our patient’s ADR.\(^10\)

As a result, although our patient had an underlying genetic predisposition for cardiac rhythm disorders, we believe that multidrug use potentiated the development of polymorphic VT without QT prolongation.

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Nil.

**Conflicts of Interest**

There are no conflicts of interest.
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