Ticagrelor-Associated Conduction Disorder: A Case Report and Review of the Literature

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Abstract

A 47-year-old female presented to emergency clinic due to non-ST-elevation myocardial infarction (NSTEMI). After receiving acetylsalicylic acid, a loading dose of ticagrelor 180 mg and intravenous unfractionated heparin, she underwent successful placement of drug eluting stent on the distal part of non-dominant left circumflex artery. The patient had no pre-existing atrioventricular (AV) block and did not use AV blocking agent. Approximately 10 h after taking a loading dose of ticagrelor, baseline normal rhythm degenerated to the first and then complete AV block, with mild dizziness. Following cessation of ticagrelor, cardiac rhythm returned to normal level within 2 days. The close monitoring of patients after starting ticagrelor is imperative, so ticagrelor may result in advanced conduction disorders. Here, we report a patient who developed various types of AV block associated with the ticagrelor taken during successful percutaneous coronary intervention for NSTEMI. We also reviewed the literature on the association between ticagrelor use and conduction abnormalities.

Keywords: Ticagrelor; Conduction abnormality; Block

Introduction

P2Y12 platelet receptor inhibitors (i.e., clopidogrel, ticagrelor and prasugrel) are the mainstay of therapy in acute coronary syndrome (ACS) at the moment \cite{1, 2}. Ticagrelor is preferred over clopidogrel for ACSs due to their more rapid and more potent antiplatelet activation \cite{3}. As well as its beneficial effects, ticagrelor may give rise to adverse events such as dyspnea and symptomatic or asymptomatic arrhythmias \cite{4}. Herein, we report a patient who developed the first degree and then complete atrioventricular (AV) block (AVB) with mild dizziness approximately 10 h after a loading dose of 180 mg ticagrelor during successful percutaneous intervention of the distal occlusion of non-dominant left circumflex artery (ndLCx) for ACS (non-ST-elevation myocardial infarction, NSTEMI). We also reviewed the literature on the association between ticagrelor use and conduction abnormalities.

Case Report

A 47-year-old female with hypertension and hyperlipidemia was admitted to emergency department due to typical angina lasting 2 days. Her blood pressure was 150/80 mm Hg. On electrocardiogram (ECG), there was a sinus rhythm with heart rate of 67 bpm, along with ST depression of 0.5 mm on inferolateral derivations (Fig. 1). Echocardiography showed hypokinesis of mid-lateral wall with an ejection fraction of 48%. We detected slightly increased cardiac troponin level. Because of ACS (NSTEMI), acetylsalicylic acid (ASA), ticagrelor (a loading dose of 180 mg and maintenance dose of 90 mg twice a day) and intravenous unfractionated heparin (10,000 IU) were given to the patient and then her coronary angiography was performed, which revealed a total occlusion of the distal ndLCx (Fig. 2a). After the lesion was predilated with 2.0 × 15 mm sized balloon catheter, a drug eluting stent of 2.5 × 23 mm was implanted and full patency was achieved (Fig. 2b). Thereafter, her symptoms dramatically improved. Since her heart rate was 67 beats/min, beta blocker therapy was not started. Approximately 10 h later, ECG showed first degree AVB without symptom (Fig. 3a). Her therapy consisting of ASA, ticagrelor, ramipril and statin was continued unchanged. On the next (second) day, the patient experienced mild dizziness with complete AVB, without hemodynamic impairment (Fig. 3b). Ticagrelor was stopped and prasugrel was initiated instead. On the third day, her ECG showed again first degree AVB without symptom (Fig. 3c). On the fourth day, she had normal sinus rhythm without AVB and symptom (Fig. 3d). On the fifth day, the patient was salubriously discharged from the hospital with therapy of ASA, prasugrel, rosvustatin and ramipril. We did not observe any heart block and/or bradyarrhythmia during the 3 months of follow-up.

Discussion

Ticagrelor is a cyclopentyltriazolopyrimidine, with a plasma half-life of approximately 6 - 12 h and, requires a daily orally administration and binding reversibly to the P2Y12 receptor \cite{4}. It provides faster and more efficacious P2Y12
Figure 1. Baseline ECG showing a sinus rhythm along with ST depression on inferolateral derivations without evidence of conduction disorder.

Figure 2. Coronary angiography showing distal occlusion of the ndLCx artery (a, white arrow), and full patency of the relevant thrombotic lesion after successful percutaneous coronary intervention (b). ndLCx: non-dominant left circumflex.

Figure 3. ECGs showing a sinus rhythm with prolonged PR interval of 260 ms approximately 10 h after taking ticagrelor loading dose (a), complete atrioventricular block on the next (second) day (b), mild first degree atrioventricular block at 220 ms after the cessation of ticagrelor on the third day (c), and normal sinus rhythm without evidence of conduction disorder on the fourth day (d).
incidence of predominately asymptomatic ventricular pauses of cardiac arrhythmias revealed an unexpected increase in the analysis post hoc. In the DISPERSE-2 (Dose Confirmation Study Assessing Anti-Platelet Effects of AZD6140 vs. Clopidogrel in Non-ST-Segment Elevation Myocardial Infarction) trial, a phase IIb Anti-Platelet Effects of AZD6140 vs. Clopidogrel in Non-ST-MMI trial, a phase IIb trial of cardiac arrhythmias revealed an unexpected increase in the analysis post hoc. In the DISPERSE-2 (Dose Confirmation Study Assessing Anti-Platelet Effects of AZD6140 vs. Clopidogrel in Non-ST-Segment Elevation Myocardial Infarction) trial, a phase IIb trial of cardiac arrhythmias revealed an unexpected increase in the analysis post hoc. In the DISPERSE-2 (Dose Confirmation Study Assessing Anti-Platelet Effects of AZD6140 vs. Clopidogrel in Non-ST-Segment Elevation Myocardial Infarction) trial, a phase IIb trial of cardiac arrhythmias revealed an unexpected increase in the analysis post hoc.

In conclusion, our report deals with the importance of awareness of the ticagrelor-related arrhythmic events as such

in patients treated with ticagrelor compared with those treated with clopidogrel [16]. For this reason, a prospective continuous ECG evaluation was carried out within the PLATO trial, and this new study (the PLATO ECG assessment) showed that those receiving ticagrelor were more likely to experience ventricular pauses than those treated with clopidogrel with no clinical importance [17]. Since this study excluded patients at an increased risk of bradycardia (known as sick sinus syndrome, first-, second- or third-degree AVB, etc.), it could not be possible to understand the actual relationship between ticagrelor use and arrhythmic events.

Although the mechanism by which ticagrelor paves the way for arrhythmias is not fully known, several potential hypotheses have been proposed. The first hypothesis is a direct effect of ticagrelor on cardiac automaticity and conduction, but this has never been noticed in pre-clinical and clinical trial on ticagrelor [17]. A second hypothesis is that ticagrelor inhibits cellular uptake and increases plasma concentration of adenosine [17, 18]. In in vitro and in vivo experiments, ticagrelor has been demonstrated to inhibit adenosine metabolism and elevate adenosine levels through prevention of adenosine uptake by erythrocytes [18]. Therefore, ticagrelor-induced increases in adenosin levels can be a reasonable explanation for the arrhythmic events observed in the cases reported. The other data supporting this hypothesis is that ticagrelor may give rise to AF. Zhang et al reported a patient with unstable angina and a history of paroxysmal AF who developed recurrent AF following ticagrelor use, and speculated that ticagrelor might provoke dormant pulmonary vein conduction and AF recurrence via increasing the levels of adenosin [12].

After the start of ticagrelor, the most important point is on the development of its side effects. There is consensus on the careful observation of patients, particularly those with already conduction disorder or those treated with one or more AV blocking drugs, after initiating of ticagrelor. Also, we recommend follow-up of patients who do not have compromised conduction system and/or do not use AV blocking agents at least during the hospital stay, because it has been shown that sinus arrest with high-degree AVB occurred in a healthy volunteer following a large dose of ticagrelor [19].

Another important point relates to what should be done after the arrhythmic adverse event due to the use of ticagrelor is observed. In general, after the drug is stopped and appropriate P2Y12 receptor inhibitor (prasugrel or clopidogrel) is started instead, the heart rhythm is observed until the normal ECG findings return. During this period, hemodynamic follow-up and/or support are provided to the patient. There is no clear information on whether or not and when the pacemaker should be inserted, if the heart rhythm does not return to normal despite this practice. In the majority of published cases, ticagrelor has been stopped with the close hemodynamic monitoring, and significant improvements have been shown on patient’s symptoms and ECG findings, as observed in our case. So far, temporary pacemaker has been required for three patients [6-8], and permanent pacemaker has been implanted for only one patient who has unresolved AVB persisting for 10 days after the discontinuation of ticagrelor [10].

In conclusion, our report deals with the importance of awareness of the ticagrelor-related arrhythmic events such as
| Author         | Age/sex | Time from ticagrelor intake to onset of cardiac arrhythmia or related symptoms | Symptoms                                                                 | ECG                                  | The underlying disease | Treatment                                      | Pre-existing conduction disease and/or AV blocking agent |
|---------------|---------|--------------------------------------------------------------------------------|--------------------------------------------------------------------------|----------|-------------------|------------------------------------------------|-------------------------------------------------|
| Nicol et al   | 39/M    | 1 h                                                                              | No                                                                       | Ventricular pause                     | STEMI - LAD           | Follow-up                                      | No/atenolol                                    |
| Goldberg et al| 52/M    | 4 h                                                                              | Syncope                                                                  | Short episodes of AVB, and ventricular pause | NSTEMI - LMCA to LCx  | Hemodynamic support and temporary pacemaker    | RBBB/bisoprolol                                |
| Goldberg et al| 71/M    | 3 h                                                                              | Syncope                                                                  | AVB, deep bradycardia, ventricular pause | STEMI - LAD           | Hemodynamic support and temporary pacemaker    | LBBB/bisoprolol                                |
| Baker et al   | 56/M    | 1 h                                                                              | Lightheadedness, diaphoresis and nausea                                   | 1 h later: borderline first-degree AVB, 3 h later: sinus bradycardia followed by sinus arrest, and complete AVB | NSTEMI - LAD           | Temporary pacemaker                            | No/no                                          |
| Ozturk et al  | 62/M    | 7 h                                                                              | No                                                                       | Mobitz tip-2 AVB                      | STEMI - RCA           | Follow-up                                      | First degree AVB/metoprolol                    |
| Unlu et al    | NA/NA   | 4 h                                                                              | NA                                                                       | Mobitz tip-2 AVB                      | ACS - LCx             | Permanent pacemaker                            | First-degree AVB/metoprolol                    |
| Sharma et al  | 55/M    | 2 months                                                                         | Fatigue and intermittent dizziness                                       | Mobitz tip-2 AVB                      | ACS - LCx             | Follow-up                                      | Moderately first-degree AVB - RBBB/metoprolol  |
| Zhang et al   | 74/M    | 6 h                                                                              | Palpitation                                                              | Atrial fibrillation                   | ACS - LAD             | Follow-up                                      | RBBB/bisoprolol                                |
| Serafini et al| 51/M    | 2 days after ticagrelor; few hours after ivabradine                             | NA                                                                       | Severe sinus bradycardia and arrest   | STEMI - LAD           | Hemodynamic support and follow-up             | RAcarvediolol and ivabradine                   |

ACS: acute coronary syndrome; AVB: atrioventricular block; ECG: electrocardiography; LAD: left anterior descending artery; LBBB: left bundle branch block; LCx: left circumflex artery; M: male; NA: not applicable; NSTEMI: non-ST-elevation myocardial infarction; RBBB: right bundle branch block; RCA: right coronary artery; STEMI: ST-elevation myocardial infarction.
sinus arrest, ventricular pause, various degrees of AVB, and AF. Extreme caution and close monitoring after initiation of ticagrelor are needed in terms of development of cardiac arrhythmias in all patients, particularly with pre-existing conduction system disorder and/or on AV nodal blocking agents.

**Conflicts of Interest**

There are no conflicts of interest related to this manuscript.

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