



CASE SERIES

Safety profile and adverse drug reactions with causality assessment of Ticagrelor in Myocardial Infraction

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ARTICLE INFO ABSTRACT



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Introduction: Antiplatelet medications are the most commonly used first-line therapy in acute coronary syndrome (ACS), particularly those undergoing percutaneous coronary intervention (PCI). P2Y₁₂ is one of the two platelet receptors for adenosine diphosphate (ADP), which play a very important role in platelet function and thrombus formation.

Method: In this article, we present 2 case reports of patients, showing severe symptoms of dyspnoea. Then we describe possible mechanisms of these complications when switching Ticagrelor to other antiplatelet drugs, and also make therapeutic recommendations for Ticagrelor-associated therapy based on what we know presently to deal with such symptoms.

Results: In ACS patients, with existing respiratory disorders, Dyspnoea can be fatal. Clinical studies have shown that reduced lung function or low EF is not harmful contraindications for Ticagrelor.

Discussion: However, these groups of patients should be monitored closely after administration of Ticagrelor.

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Introduction

Antiplatelet medications are the most commonly used first-line therapy in acute coronary syndrome (ACS), particularly for those undergoing percutaneous coronary intervention (PCI). Clopidogrel is one of the most widely prescribed antiplatelet agents that has delayed onset and mild antiplatelet action.

Ticagrelor and Prasugrel, two novel oral antiplatelet drugs, are approved as third-generation oral P2Y₁₂ inhibitors, which block platelets faster and reduce the incidence of

arterial thrombosis, as evidenced by the findings of several randomized clinical trials (Zhang *et al.*, 2020). Ticagrelor, unlike other medications (Clopidogrel and Prasugrel), does not require metabolic activation. However, an active metabolite AR-C124910XX also exhibits an effect on platelets (Krakowiak *et al.*, 2020).

P2Y₁₂ is one of the two platelet receptors for adenosine diphosphate (ADP), which play a very important role in platelet function and thrombus formation. Although it was thought to have a much more selective tissue distribution than the other platelet ADP receptor, P2Y₁, it was later



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found to be expressed in a variety of other cells, including endothelial cells, smooth muscle cells, neurons, and glial cells (Cattaneo M, 2011).

In comparison to the thienopyridine class drug clopidogrel, which inhibits P2Y₁₂ irreversibly, Ticagrelor, a direct, reversibly binding P2Y₁₂ antagonist, causes greater and more consistent inhibition of platelet function and reduces the incidence of major adverse cardiac events and total mortality in patients with acute coronary syndromes (Cattaneo M, 2011; Cattaneo M, 2010). In phase 2 investigations, Ticagrelor was associated with a 10–20 % dose-dependent incidence of dyspnoea, compared to 0–6.4 % for Clopidogrel (Husted et al., 2006; Cannon et al., 2007).

Dyspnoea has long been regarded as a difficult diagnostic and therapeutic clinical scenario in individuals with the acute coronary syndrome (ACS). In recent years, the probable link between ACS and dyspnoea has risen in popularity with the increased use of Ticagrelor in this patients because of its benefits in preventing ischemic

events and death, even though Ticagrelor can cause dyspnoea as a side effect (Steg et al., 2012; Hamm et al., 2011; Storey et al., 2011).

In this article, we present 2 case reports of patients, showing severe symptoms of dyspnoea. Then we describe possible mechanisms of these complications when switching Ticagrelor to other antiplatelet drugs, and also make therapeutic recommendations for Ticagrelor-associated therapy based on what we know presently to deal with such symptoms.

Mechanism of Action

Ticagrelor, a medication in the cyclopentyltriazolopyrimidine class, has antiplatelet effects after oral treatment. Ticagrelor which inhibits the P2Y₁₂ receptor is also involved in platelet recruitment, adhesion to collagen and von Willebrand Factor, and activation by other agonists. The P2Y₁₂ receptor inhibits the antiplatelet effects of prostacyclin.

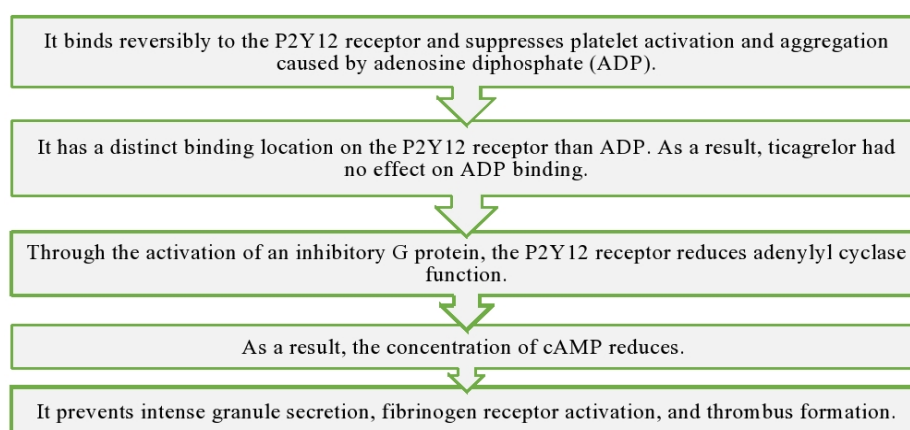


Figure 1: Mechanism of action of ticagrelor

CASE REPORT: 1

A 47 years old male patient was admitted to the cardiology department complaining of chest pain associated with vomiting episodes and sweating for a few hours. He had a past medical history of Type-II Diabetes Mellitus, Inferior Wall Myocardial Infarction for which he underwent an elective Percutaneous Trans-luminal Coronary Angioplasty in Left Anterior Descending Artery in May 2020. The patient was diagnosed with Acute Coronary Syndrome- ST-Elevated Myocardial Infarction with mild LV Dysfunction (left ventricle Dysfunction).

He was given immediate medical attention and administered a loading dose of Tab. Ticagrelor 180 mg, T. Aspirin 300 mg, and T. Atorvastatin 80 mg. He was transferred directly to the Catheterization laboratory, where emergency Coronary Artery Angiography & primary Percutaneous Coronary Intervention to the Right Coronary

Artery was performed and 2 Drug-Eluting Stent were implanted.

During the Coronary Artery Angiography procedure, the patient experienced severe dyspnoea induced by Ticagrelor unrelated to his medical condition (explained in the discussion section) and was treated with Duolin + Budecort nebulization every 8 hours. He was then transferred to ICU (Intensive care unit) and prescribed with T. Prasugrel (30 mg) loading dose followed by T. Aspirin & Prasugrel (75+10 mg) at bedtime instead of Ticagrelor. Symptoms of dyspnoea were not associated with wheezing, orthopnoea, or chest pain.

CASE REPORT: 2

A 50 years old male patient was admitted with complaints of intermittent chest pain for one day. On admission, his BP was 150/90 mmHg and his heart rate was 85 b/min. His chest examination was normal and the ECG report showed

normal sinus rhythm, left ventricular hypertrophy, QS with ST elevation in inferno-posterior leads. The patient was diagnosed with ACS-STEIPWMI, DM, and SHTN.

He was advised and taken for emergency CAG, which revealed severe RCA & LCX disease. He underwent primary PCI to distal RCA done with 1 DES. He was treated with Inj. Fondaparinux, Antiplatelets, Anti-anginal, Antacids, and other supportive cardiac drugs. Post-procedural hospital stay was uneventful and he was discharged with T. Ticagrelor, T. Aspirin, T. Nebivolol & T. Telmisartan, and T. Atorvastatin.

The patient came for review after one week with complaints of shortness of breath, which was not related to exertion. It was suggested that the severe dyspnoea was being induced by Ticagrelor and the same was replaced with T. Prasugrel. On follow up patient's dyspnoeic symptoms resolved completely.

Discussion

The goal of this study was to demonstrate that Ticagrelor can elicit particular adverse effects like dyspnoea. It is critical to recognize and distinguish these side effects from other differential diagnoses such as exacerbation of heart

failure, chronic obstructive pulmonary disease (COPD), pneumonia, anemia, or pharmacological side effects of a few drugs (such as beta-blockers) because patient care varies based on the causes. Ticagrelor inhibits the clearance of adenosine, thereby increasing its concentration in the systemic circulation, which triggers dyspnoea in patients.

In the first case, dyspnoea started 3 hours after the administration of Ticagrelor. There was no clinical, lab, or objective indication of chronic heart failure or pulmonary illnesses in this patient, which confirmed dyspnoea was induced by Ticagrelor. The patient's condition improved once Ticagrelor was stopped. To treat dyspnoea, Levolin nebulization was administered. Dyspnoea improved after replacing Ticagrelor with prasugrel in the therapeutic dose.

In case 2, the patient underwent primary PCI and after a week, he returned for a follow-up, complaining of shortness of breath. Ticagrelor-induced dyspnoea was suspected and the drug was stopped and replaced with Prasugrel 30 mg.

Naranjo probability scale of adverse drug reaction in both cases was found to be similar with a score of 6-probable. The WHO scale of adverse drug reactions in both the cases was found to be similar to a probable as given in **Figure 2** (Naranjo et al., 1981)

S.NO.	Question/Scoring Yes/No/Do Not Know or Unavailable	YES	NO	NA	CASE 1	CASE 2
1.	Are there previous conclusive reports on this reaction?	1	0	0	1	1
2.	Did the adverse event appear after the suspected drug was given?	2	-1	0	2	2
3.	Did the adverse event reaction improve when the drug was discontinued or a specific antagonist was given?	1	0	0	1	1
4.	Did the adverse reaction appear when the drug was re-administered?	2	-1	0	0	0
5.	Are there alternative causes that could have caused the reaction?	-1	2	0	2	2
6.	Did the reaction reappear when a placebo was given?	-1	1	0	0	0
7.	Was the drug detected in any body fluid in toxic, concentrations?	1	0	0	0	0
8.	Was the reaction more severe when the dose was increased/ increasing or less severe when the dose was decreased?	1	0	0	1	1
9.	Did the patient have similar reaction to the same or similar drugs in any previous exposure?	1	0	0	0	0
TOTAL					6	6

Figure 2: Naranjo probability scale of adverse drug reaction

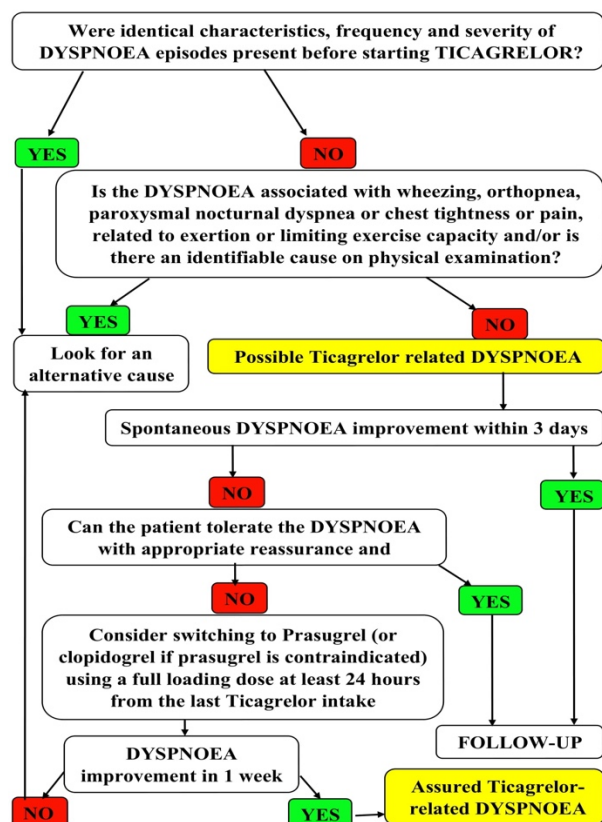


Figure 3: Guidelines for Switching Therapy

The actual mechanism of Ticagrelor-induced dyspnoea is yet to be determined. There have been several possible processes postulated (Parodi, G., & Storey, R. F. 2015).

Adenosine-Mediated Mechanism's Potential Role

Every cell contains adenosine, which is a purine nucleoside and it acts through A1, A2A, A2B, and A3 receptors (A1R, A2AR, A2BR, and A3R). The inhibitory G protein is associated with A1R and A3R, while the stimulatory G protein is associated with A2AR and A2BR. Adenosine is formed and its extracellular concentration increases dramatically after stress, hypoxia, allergic stimulation, and exercise.

Modulation of the inflammatory response, suppression of platelet aggregation, stimulation of airway afferent sensory nerve endings, and induction of bronchial smooth muscle cell contraction is the biological actions of adenosine. Extracellular adenosine has a short half-life because it is rapidly absorbed by cells via sodium-dependent and sodium-independent receptors. It is then rapidly converted to inosine or adenine nucleotides. The sodium-independent equilibrative nucleoside transporters (ENT 1/2) and adenosine absorption into cells are blocked by Ticagrelor. Ticagrelor increases the half-life of extracellular adenosine and its tissue concentration as a consequence. There's some indication that circulating adenosine levels are rising as well. According to the adenosine hypothesis, this purine

nucleoside activates vagal C fibers on the bronchial wall via the A1R and A2AR receptors, resulting in dyspnoea.

Potential Role of P2Y12 Receptor Inhibition:

This theory focuses on P2Y12 receptors rather than adenosine's influence on vagal C-fibres.

In the central nervous system, P2Y12 receptors may be found on platelets, endothelial cells, smooth muscle cells, neuron cells, and microglia. The activation of P2Y12 receptors reduces neuronal signaling by suppressing adenylyl cyclase activation and lowering cAMP levels. When P2Y12 receptors are inhibited, signaling is enhanced, which may be problematic for vagal C-fibres or glial cells. Glial cells can trigger the central chemoreflex system and elicit Cheyne–Stokes respiration.

Conclusion

In ACS patients, with existing respiratory disorders, Dyspnoea can be fatal. Clinical studies have shown that reduced lung function or low EF(ejection fraction) is not harmful contraindications for Ticagrelor. However, these groups of patients should be monitored closely after administration of Ticagrelor.

Conflict of Interest

There is no conflict of interest among authors.

Abbreviations

ACS - Acute Coronary Syndrome

ADP - Adenosine Diphosphate

PCI- Percutaneous Coronary Intervention

STEMI - ST-Elevate Myocardial Infarction

AWMI - Anterior Wall Myocardial Infarction

CAG - Coronary Artery Angiography

RCA - Right Coronary Artery

LCX - Left Circumflex Artery

DES - Drug-Eluting Stent

ACS-STEIPWMI - Acute Coronary Syndrome
ST-Elevate Posterior wall Myocardial Infarction

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