Theophylline for Attenuating Ticagrelor-Related Dyspnea

Marcelo Sanmartin-Fernandez[1] *and Jose Luis Zamorano*[1]

Hospital Universitario Ramon y Cajal - Serviço de Cardiologia,[1] *Madri - Spain*

Introduction

Dyspnea is one of the most frequent adverse reaction of ticagrelor, leading to premature discontinuation in 15-20% of the patients.[1] The mechanism is unclear, but it is thought to be related to increased tissue adenosine concentrations or to the direct reversible inhibition of $P2Y_{12}$ receptors on sensory neurons.[2]

Theophylline has been used as a bronchodilator since 1922, and its effects seem to be partly mediated through nonselective adenosine receptors blockade.[3]

The authors hypothesized that theophylline could attenuate the dyspnea caused by ticagrelor administration and reported their initial clinical experience with 10 patients.

Methods

Inclusion criteria were: 1) Presence of moderate or severe dyspnea after at least one dose of ticagrelor, not explained by cardiac or pulmonary causes; 2) Follow-up in a Cardiac Intensive Care unit; 3) Patient's formal agreement to the compassionate use of theophylline.

A single dose of 200-mg theophylline was administered, diluted in 100 ml-0.9% saline infusion over 20 min. All patients had a thorough clinical exam, electrocardiogram and echocardiogram performed before drug administration, and continuous monitoring of O_2 saturation, electrocardiogram, and noninvasive blood pressure. Electrocardiogram and echocardiograms were performed at bedside, with the sole intention of excluding alternative causes of dyspnea such as ongoing ischemia, heart failure, or bronchospasm.

Assessment of symptoms and physical exam was performed before and immediately after infusion. Each patient provided specific verbal authorization for compassionate use of theophylline in this situation. All patients granted consent for publication of anonymous data.

Results

From January/2017 to December/2019, 1,437 patients were admitted to the hospital with acute coronary syndromes, of whom 29 (3.1%) had moderate to severe dyspnea during admission presumably related to ticagrelor administration. A total of 10 patients were empirically treated with 200-mg IV theophylline because their symptoms were deemed to be sufficiently important to require therapeutic maneuvers (Table 1). The median age was 75 years (IQ range 61-80 years), six patients had previous myocardial infarctions, five patients had type 2 diabetes mellitus, four patients were smokers, and none had previous pulmonary obstructive chronic disease. In six patients, symptoms begun after orally receiving the 180-mg bolus dose, including two patients with previous administration of clopidogrel.

After theophylline administration, all patients reported attenuation of the shortness of breath, although two patients only reported a partial relief. In one of the patients with partial response, a second 200-mg bolus dose was administered one hour later with complete resolution of symptoms. All patients were treated with a different $P2Y_{12}$ inhibitor after the event. One patient (patient #3) further received 200-mg bid theophylline treatment, orally, along with ticagrelor, before the authors decided to switch to clopidogrel prior to discharge. No patient presented stent thrombosis or other thrombotic events during admission. An 82-year-old patient, with non-ST elevation myocardial infarction conservatively treated and discharged with clopidogrel, was readmitted after 20 days with a repeated myocardial infarction and cardiogenic shock and died despite successful revascularization.

Discussion

For the first time, the favorable effects of theophylline are reported in the resolution of ticagrelor-related dyspnea in patients with acute coronary syndromes. Although this initial clinical experience was strikingly positive, these findings should be considered exploratory due to the lack of a control group.

Although mechanisms behind dyspnea alleviation may be multifactorial, these preliminary findings represent a strong case for the adenosine hypothesis of dyspnea caused by reversible $P2Y_{12}$ inhibition (Figure 1). In an elegant double-blind, placebo-controlled study, Wittfeldt et al.[5] showed that a 5-mg/kg dose of theophylline attenuated the effects of an incremental adenosine infusion of 40 volunteers treated with 180-mg ticagrelor on coronary blood flow velocity and dyspnea symptoms, measured by the Borg scale. The present results extend these findings to a population of patients with acute coronary syndromes and using a smaller dose of theophylline.

Theophylline is a xanthine derivative that has been commonly used in the treatment of asthma for several decades, although its precise molecular mechanism of action is uncertain.[3,6] Among the proposed therapeutical mechanisms, it has been shown that theophylline promotes nonselective phosphodiesterase inhibition, antagonism of adenosine receptors and anti-inflammatory effects, such as interleukin-10 release, prevention of translocation of nuclear factor kappa B (NF-κB) transcription factor, and activation of histone deacetylases, which enhances

Keywords

Ticagrelor; Theophylline; Acute Coronary Syndrome.

Mailing Address: Marcelo Sanmartin Fernandez •
Servicio de Cardiologia - Hospital Universitario Ramon y Cajal - Carretera de Colmenar Viejo 9100, 28034. Madri – Spain
E-mail: msanfer@me.com
Manuscript received October 05, 2020, revised manuscript January 17, 2021, accepted February 24, 2021

DOI: https://doi.org/10.36660/abc.20201076

Table 1 – Patients' characteristics. All patients received ticagrelor as the initial antiplatelet agent with an oral bolus dose of 180 mg, except patients #8 and #9, who received clopidogrel first and then switched to ticagrelor 90 mg bid

Patient	Age (years)	Weight (kg)	Sex	Acute Coronary Syndrome	Baseline O_2 Saturation (%)	Initial $P2Y_{12}$ inhibitor	Dyspnea onset (hours after 180 mg bolus dose)	Attenuation of dyspnea	Discharge $P2Y_{12}$ inhibitor
1	56	75	Male	STEMI	98	Ticagrelor	48	Complete	Prasugrel
2	80	54	Male	STEMI	99	Ticagrelor	36	Partial	Clopidogrel
3	76	80	Female	STEMI	93	Ticagrelor	2	Complete	Clopidogrel
4	57	83	Male	STEMI	99	Ticagrelor	40	Complete	Prasugrel
5	78	68	Male	NSTEMI	97	Ticagrelor	2	Complete	Clopidogrel
6	48	85	Male	STEMI	95	Ticagrelor	12	Partial	Clopidogrel
7	71	100	Male	NSTEMI	97	Ticagrelor	2	Complete	Prasugrel
8	82	75	Male	STEMI	95	Clopidogrel	2	Complete	Clopidogrel
9	73	68	Female	NSTEMI	98	Clopidogrel	3	Complete	Clopidogrel
10	83	72	Male	NSTEMI	97	Ticagrelor	1	Complete	Clopidogrel

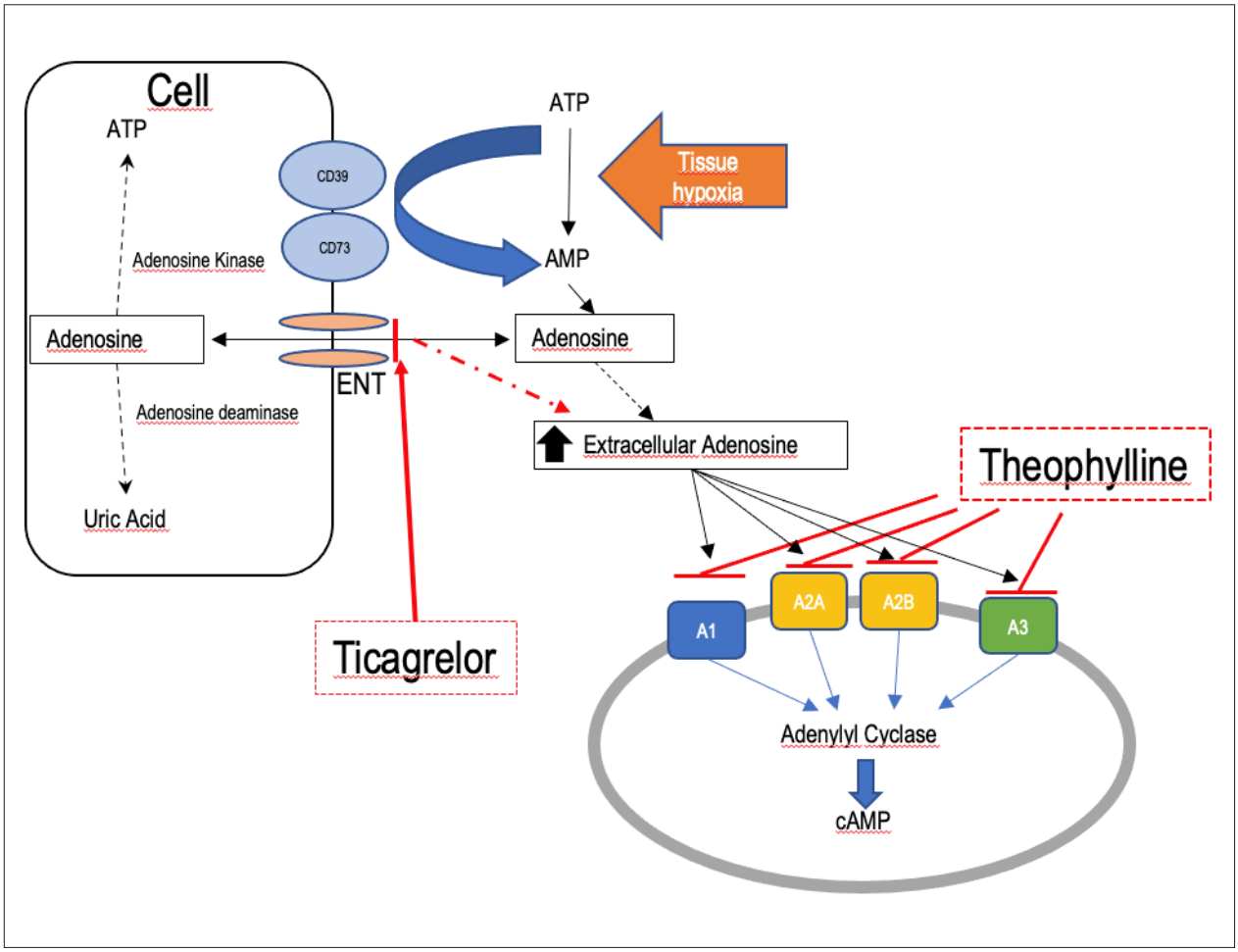

Figure 1 - *Tissue damage and hypoxia stimulates adenosine formation in extracellular space by degradation of adenosine triphosphate (ATP) and adenosine diphosphate (ADP) through the action of nucleotidases such as CD39 and CD73. Rapid degradation of adenosine intracellularly occurs by adenosine kinase and adenosine deaminase, after being taken up through sodium-independent nucleoside transporters (equilibrative nucleoside transporter (ENT)). As ticagrelor inhibits the ENT membrane, adenosine accumulates in the extracellular space, leading to adenosine-mediated effects, such as stimulation of lung neuroreceptors, probably through binding to adenosine membrane receptors (A1, A2A, A2B, and A3), and later to interaction with adenylyl cyclase and formation of cyclic adenosine monophosphate (cAMP). Theophylline blockade of adenosine receptors probably explains inhibition of adenosine-mediated effects.*[4]

the anti-inflammatory effect of corticosteroids. The authors believe that the attenuation of ticagrelor-induced dyspnea occurs through nonselective blockade of adenosine membrane receptors, preventing intracellular formation of cyclic adenosine monophosphate (Figure 1) in the interstitial lung tissue, considering that there is no objective bronchospasm or local inflammatory activity in this clinical setting.

There were no adverse effects from the theophylline administration, but the selected doses were smaller than those recommended for acute asthma (5 mg/kg). There are no reports of a prothrombotic response to theophylline. In fact, some studies suggest enhanced platelet inhibition with this drug.[7]

Although the present findings require confirmation in clinical trials, a fixed combination of theophylline and ticagrelor could represent an important step for avoiding frequent discontinuations of ticagrelor treatment.

Author Contributions

Conception and design of the research, Acquisition of data, Statistical analysis e Writing of the manuscript: Sanmartin-Fernandez M; Analysis and interpretation of the data and Critical revision of the manuscript for intellectual content: Sanmartin-Fernandez M, Zamorano JL.

Potential Conflict of Interest

No potential conflict of interest relevant to this article was reported.

Sources of Funding

There were no external funding sources for this study.

Study Association

This study is not associated with any thesis or dissertation work.

Ethics approval and consent to participate

This article does not contain any studies with human participants or animals performed by any of the authors.

References

1. Arora S, Shemisa K, Vaduganathan M, Qamar A, Gupta A, Garg SK, et al. Premature ticagrelor discontinuation in secondary prevention of atherosclerotic CVD: JACC review topic of the week. J Am Coll Cardiol. 2019;73(19):2454-64. doi: 10.1016/j.jacc.2019.03.470.
2. Unverdorben M, Parodi G, Pistolesi M, Storey RF. Dyspnea related to reversibly-binding P2Y12 inhibitors: a review of the pathophysiology, clinical presentation and diagnostics. Int J Cardiol. 2016;202:167-73. doi: 10.1016/j.ijcard.2015.08.162.
3. Biaggioni I, Paul S, Puckett A, Arzubiaga C. Caffeine and theophylline as adenosine receptor antagonists in humans. J Pharmacol Exp Ther. 1991;258(2):588-93.
4. Cattaneo M, Schulz R, Nylander S. Adenosine-mediated effects of ticagrelor: evidence and potential clinical relevance. J Am Coll Cardiol. 2014;63(23):2503-9. doi: 10.1016/j.jacc.2014.03.031.
5. Wittfeldt A, Emanuelsson H, Brandrup-Wognsen G, van Giezen JJ, Jonasson J, Nylander S, et al. Ticagrelor enhances adenosine-induced coronary vasodilatory responses in humans. J Am Coll Cardiol. 2013;61(7):723-7. doi: 10.1016/j.jacc.2012.11.032.
6. Barnes PJ. Theophylline. Pharmaceuticals. 2010;3(3):725-47. doi: 10.3390/ph3030725.
7. Hardwick RA, Hellums JD, Peterson DM, Moake JL, Olson JD. The effect of PGI2 and theophylline on the response of platelets subjected to shear stress. Blood. 1981;58(4):678-81.