Why does ticagrelor induce dyspnea?

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Summary

In studies that compared the reversible $P2Y_{12}$ inhibitor ticagrelor with the irreversible inhibitor clopidogrel, dyspnea was observed more frequently among ticagrelor-treated patients than among clopidogrel-treated patients. Because dyspnea was not associated with acidosis, pulmonary or cardiac dysfunction, alterations in the mechanisms and pathways of the sensation of dyspnea may be involved in its pathogenesis. It has been hypothesised that the sensation of dyspnea in ticagrelor-treated patients is triggered by adenosine, because ticagrelor inhibits its clearance, thereby increasing its concentration in the circulation. However, dipyridamole, a much stronger inhibitor of adenosine clearance than ticagrelor, usually does not cause dyspnea. We hypothesise that inhibition of $P2Y_{12}$ on sensory neurons increases the sensation of dyspnea, particularly when reversible inhibitors are used. We base our hypothesis on the following considerations: 1) cangrelor and elinogrel, which, like ticagrelor, are reversible $P2Y_{12}$ inhibitors, also increase the incidence of dyspnea; 2) it is biologically plausible that inhibition of $P2Y_{12}$ on sensory neurons increases the sensation of dyspnea; 3) inhibition of $P2Y_{12}$ on platelets (which do not have a nucleus) by clopidogrel is permanent, despite the once daily administration and the short plasma half-life of the inhibitor; 4) in contrast, inhibition of $P2Y_{12}$ on neurons by clopidogrel may be temporary and transient, because neurons have a nucleus and can therefore rapidly replace the inhibited receptors with newly synthetised ones; 5) inhibition of $P2Y_{12}$ on neurons by reversible inhibitors is permanent, because the plasma drug concentration is maintained high by repeated dosing, in order to ensure permanent inhibition of platelet $P2Y_{12}$.

Keywords

ADP receptors, arterial thrombosis, nervous system

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Introduction

$P2Y_{12}$ is one of the two platelet receptors for adenosine diphosphate (ADP), which play a very important role in platelet function and thrombus formation (1). Although it was initially considered to have a much more selective tissue distribution than the other platelet ADP receptor, $P2Y_1$, it was later shown to be expressed in many cell lines, including endothelial cells, smooth muscle cells, neurons and glial cells (1). Drugs that target $P2Y_{12}$ reduce the incidence of arterial thrombosis, as documented by the results of several randomised clinical trials (1, 2).

Compared to the thienopyridine drug clopidogrel, which irreversibly inhibits $P2Y_{12}$, ticagrelor, a direct, reversibly binding $P2Y_{12}$ antagonist, causes greater and more consistent inhibition of platelet function, and decreases the incidence of major adverse cardiovascular events (MACE) and total mortality in patients with acute coronary syndromes (ACS) (1, 2).

Dyspnea is a relatively frequent adverse event of ticagrelor therapy (3–8). In all the studies in which ticagrelor and clopidogrel were compared, the frequency of ticagrelor-associated dyspnea was higher, compared to that associated with clopidogrel (►Table 1). In phase 2 studies, ticagrelor was associated with a dose-dependent incidence of dyspnea of 10 to 20%, compared to 0–6.4% with clopidogrel (4, 5). In the ONSET/OFFSET study, which evaluated the onset and offset of the antiplatelet effects of ticagrelor compared with clopidogrel and placebo in patients with stable coronary artery disease (CAD) (6), dyspnea occurred in 38.6%, 9.3% an 8.3% in the ticagrelor, clopidogrel and placebo groups and was judged by the investigator to be likely or possibly due to the study drug in 24.6%, 3.7% and 0% (7). The frequency of dyspnea was 13% with ticagrelor and 4% with clopidogrel in the RESPOND study, which, using a cross-over design, tested the ability of ticagrelor to inhibit $P2Y_{12}$-dependent platelet function in patients who were non-responders to clopidogrel (8). Finally, the PLATO study, a multicenter, double-blind, randomised trial, comparing ticagrelor and clopidogrel for the prevention of MACE in patients with ACS, reported 13.8% dyspnea associated with ticagrelor versus 7.8 % associated with clopidogrel (3).

Ticagrelor-associated dyspnea was reported to be mild to moderate in nature, disappearing after drug withdrawal and rarely determining drug discontinuation of affected patients (3–5, 7–9).

Causes of dyspnea

Dyspnea has many causes, including pulmonary, cardiac and metabolic diseases (14). In-depth studies of pulmonary and car-

diac function in patients with ACS or stable CAD treated with ticagrelor or clopidogrel concluded that dyspnea was not associated with drug-induced pulmonary dysfunction (7,15), cardiac dysfunction or acidosis (7). Moreover, patients with a prior history of congestive heart failure, chronic obstructive pulmonary disease, or other causes of dyspnea do not appear to be more likely to develop ticagrelor-related dyspnea compared with those without a history of these conditions (7). It is then possible that alterations of the mechanisms and pathways of the sensation of dyspnea are involved in its pathogenesis.

Recent evidence suggests that a perturbation in the ventilatory response generates afferent information from vagal receptors in the lungs (and possibly mechanoreceptors in the respiratory muscles) to the sensorimotor cortex and results in the sensation of dyspnea (16). Studies in humans and experimental animals indicate that adenosine is dyspnogenic and that its effect is mediated by activation of vagal C fibers (16). Most likely based on these observations, a frequently purported, tentative explanation for dyspnea during treatment with ticagrelor is that it may be caused by increased levels of extracellular adenosine. This compound is physiologically increased in the extracellular environment in response to high cellular energy demands and low oxygen supply, but is rapidly taken up into the cells by nucleoside transporters: ticagrelor has been shown to inhibit adenosine uptake possibly by inhibiting a sodium-independent equilibrative nucleoside transporter, most likely ENT1 (17), thereby prolonging its half-life in the extracellular environment. However, although this tentative explanation is indeed captivating, it seems inadequate to wholly account for the increased incidence of dyspnea in patients receiving ticagrelor. Dipyridamole is a potent adenosine uptake inhibitor, approximately one order of magnitude more potent than ticagrelor (17), yet dyspnea associated with its use has never been reported in the several randomised clinical trials in which the drug was orally administered to patients at risk for coronary or cerebrovascular accidents. Moreover, the incidence of dyspnea among 3,911 patients undergoing intravenous dipyridamole-thallium imaging for the evaluation of CAD was only 2.6%, despite the acutely intravenously administered high dose of the drug, and was usually associated with chest discomfort, headache, dizziness and electrocardiogram abnormalities, which were generally more frequent than dyspnea itself (18).

Hypothesis: ticagrelor-induced dyspnea is mediated by inhibition of the $P2Y_{12}$ receptors

The hypothesis that the pathogenesis of dyspnea during ticagrelor treatment is mediated by the main mechanism of action of the drug, i.e. inhibition of the $P2Y_{12}$ receptor (expressed by cells different from platelets), has never been considered or suggested, probably based on the assumption that clopidogrel, which is also an inhibitor of $P2Y_{12}$, is not associated with this adverse effect. Indeed the incidence of dyspnea was not different in clopidogrel-treated patients and aspirin-treated patients in the CAPRIE study (14). However, after the first demonstration that treatment with ticagrelor is associated with a high incidence of dyspnea (4), all the following studies that compared ticagrelor with clopidogrel did show that dyspnea is an, albeit rarer and milder, adverse effect also of clopidogrel treatment (▶Table 1). Because pulmonary, cardiac and metabolic diseases that are associated with dyspnea may be common among patients with ACS, the critical point is to identify those cases of dyspnea that are not attributable to these conditions. In the PLATO and ONSET/OFFSET studies, dyspnea was considered "unexplained" (i.e. not attributed to suspected aetiologies) or "likely or possibly due to the study drug" in 27.3% (366/1339) (9) and 63.3% (14/22) (6) of ticagrelor-treated patients, and in 20.1% (160/798) (9) and 40% (2/5) (6) of clopidogrel-treated patients. Similarly, Serebruany et al. showed that, among 3,719 patients who underwent coronary stenting, 157 (4.2%) developed dyspnea while on treatment with clopidogrel, which was attributable to underlying pulmonary or cardiac diseases in most instances, but remained unexplained in 17/157 (10.8%) (14). Moreover, 13 patients in the PLATO study (9) and 10 patients in the Disperse-2 study (5) had to discontinue clopidogrel treatment, due to the severity of dyspnea. In conclusion, we think that, based on the available published evidence, it is likely that clopidogrel may cause dyspnea in a small proportion of treated patients. Therefore, although we acknowledge that dyspnea does not appear to be a relevant clinical problem associated with clopidogrel treatment, the published reports do not oppose our hypothesis that inhibition of $P2Y_{12}$ may increase the sensation of dyspnea.

Based on this hypothesis, one may argue that the lower incidence of clopidogrel-associated dyspnea, compared to ticagrelor, could be due to the fact that clopidogrel does not adequately inhibit $P2Y_{12}$ in about 30% of patients (1, 2). However, this hypothesis is not completely supported by the observation that in the TRITON TIMI 38 trial (19) the frequency of dyspnea among patients treated with prasugrel, which, like ticagrelor, adequately inhibits $P2Y_{12}$ in the vast majority of treated patients (2), was only about 1.10-fold higher than that observed among clopidogrel-treated patients (4.9% vs. 4.5%) (20). Based on these data, it appears reasonable to conclude that the more efficient inhibition of $P2Y_{12}$ by ticagrelor may only partially account for the much higher incidence of dyspnea observed in ticagrelor-treated patients, compared to clopidogrel treated patients (1.64– to 4.17-fold higher, ▶Table 1).

Certainly more enlightening, albeit often overlooked in the literature, are the data from recent clinical trials, which demonstrate that, similarly to ticagrelor, two other $P2Y_{12}$ inhibitors, cangrelor (10) and elinogrel (11), are associated with an incidence of dyspnea that is 2.5– to 3.3-fold higher compared to clopidogrel (▶Table 1). Although it cannot be formally ruled out, it is unlikely that three drugs with different molecular structures (elinogrel, in particular, belongs to a different structural family of non-nucleotide antagonists), which were developed to inhibit $P2Y_{12}$, all share the same side effect of inhibiting adenosine uptake. At any rate, no reports have demonstrated that either cangrelor or elinogrel does so. We consider more probable that these three drugs (and, perhaps, albeit to a lesser extent, clopidogrel) increase the incidence of dyspnea through their main mechanism of action, i.e. inhibition of the

$P2Y_{12}$ receptor. The characteristic that unites ticagrelor, cangrelor and elinogrel is that they are reversible inhibitors of $P2Y_{12}$, at variance with clopidogrel, which inhibits the receptor irreversibly.

Based on these considerations, we hypothesise that drugs inhibiting $P2Y_{12}$ increase the incidence of dyspnea, particularly if they reversibly inhibit the receptor. In the following paragraphs we will attempt to demonstrate that this hypothesis is biologically plausible.

Is it biologically plausible that drugs inhibiting the $P2Y_{12}$ receptor increase the incidence of dyspnea?

As previously mentioned, dyspnea can be induced via central mechanisms, chemoreceptors or stimulation of afferent vagal C-fibers (16). $P2Y_{12}$ was shown to be expressed in neuronal tissues and to inhibit neuronal signaling, through the inhibition of cyclic adenosine monophosphate (cAMP) generation (21, 22). Therefore, it can be predicted that inhibitors of $P2Y_{12}$ will increase neuronal signalling. Indeed, Kubista et al. showed that cangrelor antagonises the inhibition of neuronal Ca^{2+} channels by adenine nucleotides, which is mediated by $P2Y_{12}$ and paralleled by inhibition of cAMP accumulation (23). The importance of cAMP in the activation of afferent C-fibers is highlighted by the effect of prostaglandin E_2 (PGE_2), which potentiated hyperthermia-induced hypersensitivity of vagal pulmonary C-fibers through its interaction with Gs-coupled EP2 and EP4 receptors (24). Moreover, inhalation of PGE_2 aerosol significantly increased the dyspnoic sensation during exercise in healthy human subjects, without inducing changes in airway resistance or lung volume (25). Since $P2Y_{12}$ is negatively coupled to adenylyl cyclase, its inhibition should enhance the effects of PGE_2, as much as it enhances the antiplatelet effects of prostacyclin, which is also mediated by increased cAMP levels (26).

In conclusion, experimental evidence indicates that it is biologically plausible that inhibition of $P2Y_{12}$ increases the conductivity of vagal C-fibers and, hence, the sensation of dyspnea.

Is it biologically plausible that reversible $P2Y_{12}$ inhibitors cause dyspnea more commonly than the irreversible inhibitor clopidogrel?

Adequate and constant blood levels of reversible inhibitors must be maintained in order to achieve an adequate and constant degree of inhibition of the platelet $P2Y_{12}$ receptors. The dose and frequency of their administration depend on their pharmacodynamic and pharmacokinetic properties. Ticagrelor and elinogrel, whose half-lives are about 8–12 hours (27, 28), are given twice daily, (3, 29) while cangrelor, which is a parenteral drug with a very short half-life (<10 minutes) (28), is administered by continuous intravenous infusion. Maintaining adequate blood levels of the drug will not only inhibit the $P2Y_{12}$ receptors that are expressed on platelets, but

Table 1: Comparison of the incidence of dyspnea in patients treated with reversible $P2Y_{12}$ inhibitors and patients treated with clopidogrel.

Study drug (reversible $P2Y_{12}$ inhibitor)	Patients (total n)	Dose	Duration of treatment	A Percent of dyspnea in study drug group	B Percent of dyspnea in clopidorel group	A/B	Study (reference)
Ticagrelor*	Patients with atheroslerosis (200)	50 mg b.i.d. 100 mg b.i.d. 200 mg b.i.d. 400 mg q.d.	28 d 28 d 28 d 28 d	10 10 16 20	0 0 0 0	∞ ∞ ∞ ∞	DISPERSE (4)
Ticagrelor	NSTE-ACS (990)	90 mg b.i.d. 180 mg b.i.d.	12 wk 12 wk	10.5 15.8	6.4 6.4	1.64 2.47	DISPERSE-2 (5)
Ticagrelor#	Stable CAD (123)	90 mg b.i.d.	6 wk	38.6	9.3	4.15	ONSET/OFFSET (6,7)
Ticagrelor	Stable CAD (98)	90 mg b.i.d.	14 d	13	4	3.25	RESPOND (8)
Ticagrelor	ACS (18,624)	90 mg b.i.d.	12 mo	13.8	7.8	1.77	PLATO (3)
Cangrelor§	ACS (8,877)	4 µg/Kg/min IV	2–4 h	1	0.4	2.5	CHAMPION-PCI (10)
Elinogrel	Nonurgent PCI (626)	100 mg b.i.d. 150 mg b.i.d.	120 d 120 d	12.4 12.1	3.8 3.8	3.26 3.18	INNOVATE-PCI (11)

Clopidogrel was given at the maintenance dose of 75 mg q.d. Variable loading doses of reversible $P2Y_{12}$ inhibitors and clopidogrel were administered to patients in all studies, with the exception of DISPERSE. *The formulation of ticagrelor that was used in this study was different from that used in the other studies listed in this table: 100 mg of this formulation are equivalent to 90 mg of the other formulation. #In this study, ticagrelor was compared also to placebo. The frequency of dyspnea in placebo-treated patients was 8.3%. The drug-attributable frequency of dyspnea, according to the judgment of the investigators, was 24.6%, 3.7% and 0% for ticagrelor, clopidogrel and placebo. §Cangrelor was tested also in two additional randomised clinical trials, CHAMPION-PLATFORM (12) and BRIDGE (13), in which it was compared to placebo. The frequency of dyspnea in cangrelor-treated patients was 1.4 and 1.9, compared to 0.5 and 1.0 in placebo treated patients: therefore, the frequency of dyspnea in cangrelor-treated patients was 2.8-fold and 1.9-fold higher than in placebo-treated patients. CAD: coronary artery disease; ACS: acute coronary syndrome; NSTE: non ST elevation; b.i.d.: twice daily; q.d.: once daily.

also those that are expressed on other cells, like, for instance, neurons. Therefore, ticagrelor, elinogrel and cangrelor, at the dose regimens that have been used, could constantly inhibit $P2Y_{12}$ receptors on sensory neurons, thereby increasing the dyspnea sensation.

Clopidogrel is a pro-drug that needs to be metabolised *in vivo* by hepatic cytochrome-P450 isoenzymes to its active metabolite (AM), which forms a disulfide bond with cysteine residues on $P2Y_{12}$, thereby irreversibly inhibiting the receptor (2). Since platelets are anucleated cells, they cannot replace the inhibited receptors with newly synthetised ones and will remain inhibited for their entire lifespan. In contrast, in all other cells expressing the receptor, inhibition of $P2Y_{12}$ by clopidogrel-AM during its very short appearance in the circulation (30), would only be temporary and transient, because cells will rapidly replace the inhibited receptors with newly synthetised ones. In particular, *in vitro* experiments demonstrated that newly synthesised proteins can be detected within few minutes since the start of observation, both in the somata and dendrites of neurons (31). Therefore, $P2Y_{12}$ on sensory neurons could very transiently be inhibited by clopidogrel-AM, accounting for the very low frequency of dyspnea that is associated with its administration.

In conclusion, differences between the pharmacological properties of reversible $P2Y_{12}$ inhibitors and clopidogrel, in association with differences in biology of anucleated platelets and nucleated $P2Y_{12}$ bearing neurons, could account for the higher incidence of dyspnea observed during treatment with reversible inhibitors, compared to clopidogrel. More in general, considering that the presence of $P2Y_{12}$ on nucleated cells is more widespread than initially believed, this model could account for differences in the pharmacological responses to thienopyridines compared to reversible $P2Y_{12}$ inhibitors (▶ Fig. 1), not only in terms of incidence of untoward side effects, but also in terms of clinical efficacy.

Why is ticagrelor-induced dyspnea transient?

A remaining issue to be explained concerns the transient nature of dyspnea in most patients, despite continuous administration of ticagrelor. This could be explained by the fact that the intensity of the sensation of dyspnea is determined by a mismatch between the new afferent/efferent information and a sort of "memory" in the cortical centers of "normal" afferent input and "normal" respir-

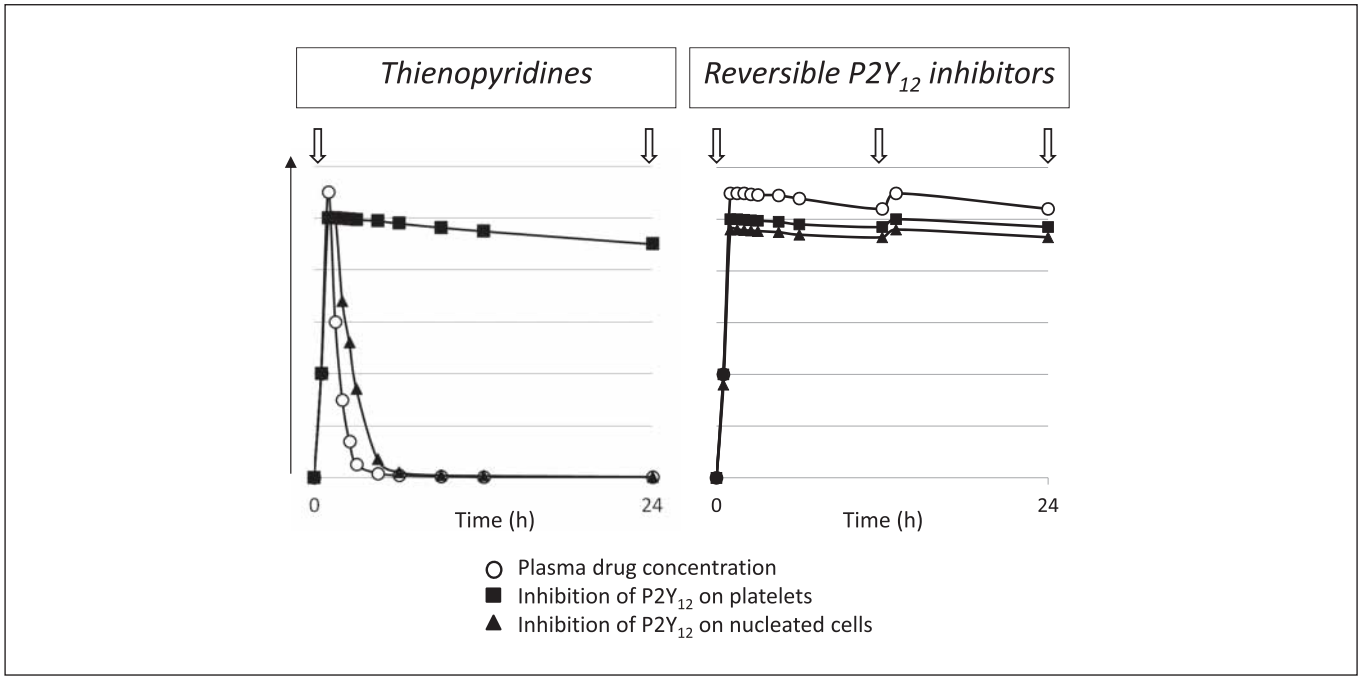

Figure 1: Differences in the pharmacokinetics (PK) and pharmacodynamics (PD) of thienopyridines, which irreversibly inhibit the $P2Y_{12}$ receptors, and reversible inhibitors of $P2Y_{12}$. The continuous inhibition of $P2Y_{12}$ on nucleated cells by reversible inhibitors of the receptor, as opposed to its transient inhibition by thienopyridines may account for differences in the pharmacological responses to the drugs, not only in terms of incidence of untoward side effects, but also in terms of clinical efficacy. The hypothesis that we raise in this manuscript is that continuous inhibition of $P2Y_{12}$ on sensory neurons (which are nucleated cells) by reversible $P2Y_{12}$ inhibitors accounts for the higher incidence of dyspnea in patients treated with reversible inhibitors, compared to clopidogrel (see text for details). Values in the graph are not based on real data and should be considered illustrative. Values of PK of thienopyridines are inspired by the data shown in [35]; PD data of thienopyridines account for a theoretical decrease of inhibition of the platelet $P2Y_{12}$ receptors of about 10% at 24 hours post dosing, due to the appearance of about 10% (6), newly formed, non-inhibited platelets in the circulation. PD data of reversible $P2Y_{12}$ inhibitors are inspired to the PD data of ticagrelor, reported in the ONSET-OFFSET study (6). Arrows at the top of the graphs indicate the times of administration of the drugs.

atory system response, in terms of effort required to achieve a given airflow or ventilation (16). After some days of treatment with ticagrelor, the new afferent/efferent information, determined by the hyperactivity of sensory neurons, will be retained as a new "memory" by the cortical centers, which will be unable to recognise them as new or pathological.

Conclusion

In conclusion, we think that inhibition of $P2Y_{12}$ on C fibers of sensory neurons is responsible for the observed incidence of dyspnea in patients treated with antiplatelet drugs that target $P2Y_{12}$. The much higher incidence of dyspnea that has been observed in patients treated with ticagrelor or other drugs that reversibly bind to the receptor, than in patients treated with the irreversible inhibitor clopidogrel, is likely explained by differences in pharmacokinetic properties of these drugs. In contrast, differences in the inhibitory efficiency of the drugs seem to play a marginal role. In fact, the incidence of dyspnea in patients treated with clopidogrel is only slightly lower than in patients treated with prasugrel, which is a more efficient, irreversible $P2Y_{12}$ inhibitor than clopidogrel.

We are aware that we are purporting a hypothesis that is difficult to test for at least two reasons: i) the definition of the precise physical stimulus that causes dyspnea is problematic (32); ii) dyspnea is a sensation that can only be properly assessed in collaborating human beings (16) (these difficulties likely explain why previous pathogenic hypotheses that have been published [33] have not been successfully tested yet). Due to these difficulties, and considering that C fibers can react to various stimuli, which may be thermal, mechanical or chemical in nature (34), we are planning to test our hypothesis in preliminary experiments, in which the effects of different $P2Y_{12}$ inhibiting drugs on surrogate end-points, such as thermal and tactile sensations, will be measured.

Conflicts of interest

None declared.

This article reflects the view of its author(s) and is not representative of the view of the Editorial Board or the Publishers.

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