'Reversible nature of platelet binding causing transfusion-related acute lung injury (TRALI) syndrome may explain dyspnea after ticagrelor and elinogrel’ – a hypothesis that remains unproven


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The clinical introduction of the reversible-type P2Y12-ADP-receptor antagonist ticagrelor has added progress to our management of acute coronary syndromes (1) but also resulted in the appearance of new side-effects, which at a first view, seem unrelated to its inhibition of platelet function. In addition to bradycardias, which was dyspnoea which occurred in a significant proportion (≥10%) of ticagrelor-treated patients (2).

These side-effects were previously not reported after blockade of the P2Y12 ADP-receptor by irreversible type antagonists, such as clopidogrel or prasugrel. This suggested that the reversibility of binding, i.e. the presence of not platelet-bound active drug and/or its active metabolite (AR-C124910XX) might be involved, allowing for redistribution of the active compound and/or active metabolite between all circulating platelets (3) but also translocation to other non-platelet targets, eventually resulting in "off target" effects. The high-level (>99.8%) protein-binding of both ticagrelor and its active metabolite (4) in this context might act as a "storage pool" and keep the active agents within the circulation for several hours. Redistribution of ticagrelor between circulating platelets has also been considered to contribute to the reduction in cardiovascular mortality in the PLATO trial (3) and might also become relevant in clinical conditions if the antiplatelet effect of ticagrelor needs to be antagonised, for example, in urgent surgery procedures by infusion of external donor platelets.

A similar, though less clear incidence of dyspnoea has also been suggested for the ATP-analog cangrelor, another reversible-type P2Y12-ADP-receptor antagonist but also the reversible-type inhibitor, elinogrel which caused dyspnoea in a significant percentage of patients in the INNOVATE-PCI trial (5). This compound has no structural relationships to ticagrelor or cangrelor, respectively. This supports the concept of reversibility of binding of the compounds to the platelets per se as an essential precaution for non-target side effects of these compounds but is not sufficient to explain any "off-target" pharmacodynamic effects.

In this issue of Thrombosis and Haemostasis, V. L. Serebruany (6) puts forward an interesting, though speculative, hypothesis, about the induction of dyspnoea by reversibly-acting P2Y12-ADP receptor antagonists. Serebruany (6) suggests that dyspnoea after ticagrelor and other reversible type ADP-antagonists such as elinogrel may not be caused by "off-target" effects of these drugs but rather results from “exhaustion” of platelets after repeated platelet receptor occupancy and associated onset-offset reactions as opposed to the permanent blockade of the receptor by clopidogrel-like compounds (6). According to this hypothesis, repeated daily cycles of binding and unbinding of a platelet ligand ultimately might disturb the intra-platelet balance between pro-survival Bcl-xL and proapoptotic Bak (7), eventually resulting in premature apoptosis and platelet destruction. These “exhausted” platelets may be considered as "foreign" by body defense mechanisms and trigger systemic autoimmune responses. In addition, potentially toxic products are released from apoptotic platelets which – in a second-step procedure – may activate white cells and finally cause transfusion-induced acute pulmonary injury (TRALI)-like symptoms, including dyspnoea.

An association of TRALI with blood products is well known and was originally described as a complication of aged blood products in patients at poor medical conditions. If these patients get blood transfusions, lipids and cytokines from stored blood products, i.e. platelets and white cells, may be released and, in a second step then directly activate neutrophils and cause pulmonary injury (8). However, recent data suggest that among TRALI-inducing transfusion-related risk factors, platelets as single cells were only involved in 6% of cases and even infusion of "aged" platelets stored for more than four days did not increase the risk of TRALI (9).

Finally, the incidence of TRALI has been reported to be 0.81 (95% confidence interval: 0.44–1.49) per 10,000 blood transfusions (9) and, therefore, much less frequent than ticagrelor-associated dyspnoea, occurring in 5–15% of cases in the different
trials – and 14.5% in PLATO (2). Thus, the pathophysiology, symptoms and frequency of “real” TRALI differ in many aspects from ticagrelor-related pulmonary dysfunction, although an association cannot be completely excluded.

If the onset/offset binding of antiplatelet compounds was important, then other reversible-type antagonists should exhibit similar effects. However, there are no data on this. On the contrary, various anti-integrin-type, reversible GP IIb/IIIa receptor blockers, such as tirofiban, epifibatide and abciximab – though with a different mode of antiplatelet action, will rather stimulate than inhibit platelet function by outside-in signalling (10), but have not been reported to exhaust platelets or to cause dyspnoea, except as a secondary consequence to alveolar haemorrhage after overdosing.

What are the alternative explanations for ticagrelor-related dyspnoea? One, frequently cited hypothesis is that many if not all "off-target" side-effects of ticagrelor are adenosine-like, either due to an adenosine-mimetic action of the compound itself because of its adenosine-nucleoside backbone or by amplifying adenosine responses. In fact, most (if not all) of the non-bleeding-related clinically relevant side-effects of ticagrelor, including dyspnoea, bradycardia and renal dysfunction could be related to an adenosine-like action on adenosine A1 and A2A-receptors.

Serebruany himself had discussed this possibility previously, although he also clearly stated that no definite data were available to support the hypothesis (11). Ticagrelor-induced inhibition of adenosine uptake by red cells (12) will amplify adenosine-like actions additionally. This was recently demonstrated in a trial on healthy volunteers, showing that theophylline-sensitive dyspnoea, a clinical condition induced by infusion of increasing doses of adenosine to healthy volunteers and mediated via adenosine A1 receptors, was significantly more severe in the presence of a standard loading dose of 180 mg ticagrelor than after placebo (13).

Importantly, there are no structural similarities between adenosine and elinogrel which also caused dyspnoea in the INNOVATE-trial (5). This possibly excludes pharmacodynamic actions of the compound because of a similar chemical structure. However, structural similarities are not always a precaution for similar pharmacodynamic actions. For example, lumiracoxib an acidic cyclooxygenase (COX)-2 selective inhibitor has nothing in common chemically with the "conventional" selective non-acidic coxibs rofecoxib or etoricoxib but is the most selective and potent COX-2 inhibitor currently known (14).

The viewpoint by Serebruany (6) concludes that if the adenosine hypothesis of ticagrelor-induced dyspnoea is challenged, it is completely unclear how to explain the survival benefit in the PLATO-trial, comparing ticagrelor with clopidogrel in patients with acute coronary syndrome (ACS) (6). No such benefit was seen in the TRITON-study with prasugrel in a similar group of patients (15). This is not the place to discuss this issue in more detail, although it is a clinically very relevant issue, specifically if one considers the cardioprotective actions of adenosine. Unsurprisingly, Serebruany has already tried to provoke such debate (16–18).

It should be noted that PLATO – as opposed to the TRITON trial with prasugrel – did include 39% medically treated patients, who tended to respond better and had a lower bleeding risk than those subjected to percutaneous coronary intervention (PCI) (hazard ratio: 0.78 vs. 0.88). The recently locked TRILOGY study in medically managed ACS patients will show whether the overall clinical result in these patients on prasugrel differs from that in TRITON where all patients (99%) were subjected to acute PCI. Finally, all patients in PLATO and also the TRITON-trial were on aspirin which at "high" dose (≥300 mg/day) appears to differentially modify the clinical benefit of ACS patients treated with ADP-antagonists: reduction with ticagrelor (19), no change with prasugrel (20) and improvement with clopidogrel (21). In any case, dyspnoea in the PLATO trial was usually mild or moderate in intensity and did not appear to be associated with differences in efficacy or safety outcome (2).

In conclusion, the definition of ticagrelor-related dyspnoea as a TRALL-like disease, caused by exhausted platelets and their action as immunogens on the lung is an interesting hypothesis, but definitely requires experimental support and much more data to become substantiated. According to the current data – whatever the mechanism of ticagrelor-related dyspnoea is – this adverse effect does not influence the clinical outcome of ACS patients.

Conflicts of interest
K. Schrör is member of Advisory Boards of Bayer and Daiichi-Sankyo/Lilly and has received honoraria for lectures from these companies as well as Astra-Zeneca.

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References