Letters to the Editor

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Dyspnoea after AZD6140: safety first?

Husted et al.1 published dose-finding Phase 2 randomized study comparing novel oral reversible platelet P2Y12 antagonist, AZD6140, with conventional clopidogrel on top of low-dose aspirin. The authors should be acknowledged for the thoughtful design, detailed analysis, well-balanced opinions, and perfect timing for such work to appear. Indeed, the era of expanding antiplatelet regimens and indications may require new agents as the substitutes or additions to the available strategies. However, the alarming frequency of dyspnoea reported in the paper1 (Table 5) was not mentioned in the abstract or tried to be explained in the discussion. In fact, at least 10% for the lower doses and up to 20% of patients treated with the highest dose of AZD6140 experienced dyspnoea.

The association between treatment with antithrombotic agents and dyspnoea is not new. Few anecdotal observations suggested that aspirin,2 hirudin,3 or eptifibatide4 might cause dyspnoea, although such side effects are extremely rare. It seems that the immune conflict between the hostile platelet receptors subjected to the reversible blockade by the antiplatelet agent(s) may lead to the mild episodes of thrombotic thrombocytopenic purpura and consequent fluid retention contributing to dyspnoea. Being the first ever oral platelet glycoprotein IIb/IIIa antagonist to be tested in the clinical trials as an antiplatelet agent, and especially because of its reversible nature, AZD6140 may appear to be safe for the intact platelets in the pre-clinical studies, but hurt already activated platelets during the unbinding from the cell surface in patients with vascular disease, as was previously documented for the oral platelet glycoprotein IIb/IIIa inhibitors.5 Lack of dyspnoea episodes after clopidogrel or prasugrel, which are irreversible P2Y12 receptor inhibitors also indirectly supports this hypothesis. Additional pulmonary function tests, immunological and platelet receptor studies are needed to determine the cause of dyspnoea after AZD6140 and to figure out how such serious adverse reaction can be prevented or at least minimized. Last but not least is the fact that clopidogrel replaced ticlopidine based not on the superior efficacy, or more potent platelet inhibition, but because of the better safety profile.

In conclusion, although the initial clinical results with AZD6140 are promising, the unusually high incidence of dyspnoea is not an artefact. Such serious adverse reaction requires straightforward acknowledgement, much better understanding, and possible prevention plan, especially in the chronic long-term setting.

References


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Dyspnoea after AZD6140: safety first?: reply

I would like to thank Dr Serebruany for his interest in our manuscript. In his letter, he expressed concern about the adverse event of dyspnoea reported in the Phase 2a study of the reversible, oral P2Y12 antagonist, AZD6140.1 Results describes the 23 patients with reported dyspnoea, none of which was considered serious and only one patient discontinued therapy due to this adverse event. Most of these events did not trigger further diagnostic evaluations and were not thought by the investigators to be related to heart failure or bronchospasm. Further investigation of AZD6140 has occurred in DISPERSE II, a Phase 2b study with longer exposure in 990 patients with non-ST elevation ACS.2 This second study confirms that dyspnoea occurs more frequently with AZD6140 than with clopidogrel. The clinical impact again appeared low with few cases in either group being considered serious or leading to discontinuation of therapy. The incidence of new cases reduced after 30 days.

Dr Serebruany also speculates on potential mechanisms for the dyspnoea. Dyspnoea is a non-specific symptom that has been occasionally reported both with aspirin and clopidogrel,3 but except for ASA-induced asthma, and is probably not causally related to these agents. The examples given for hirudin and eptifibatide similarly are more likely related to the underlying condition than to the antithrombotic per se. No thrombocytopenia has been observed with any of the AZD6140 cases of dyspnoea in studies to date, so there is no evidence to support thrombotic thrombocytopenic purpura as a mechanism. Furthermore, there is no reason to believe that reversible blockade of the P2Y12 receptor would lead to ‘immune conflict’ as postulated by Dr Serebruany. Covalent binding of the thienopyridine active metabolite to the P2Y12 receptor would be more likely to lead to structural changes in the receptor and subsequent immunological response. Neither fluid retention (or other signs of heart failure) nor bronchospasm has been reported as the mechanism for dyspnoea by investigators.

Because AZD6140 is pharmacologically different from the oral platelet glycoprotein IIb/IIIa inhibitors, it would be inappropriate to expect similar harmful effects on platelet function. Increased expression of the platelet glycoprotein IIb/IIIa inhibitors is seen during GPIb/IIa treatment means that platelets still activate and degranulate6, whereas P2Y12 antagonists reduce activation as shown by Quinton et al., using cangrelor in vitro and by Storey et al., using blood from cangrelor and clopidogrel treated patients. GPIb/IIa antagonists reduce the aggregation of platelets activated by any stimulus, whereas P2Y12 antagonists reduce initial activation and subsequent aggregation, which should lead to a more favourable therapeutic effect.

As stated in Discussion of the paper and as suggested by Dr Serbruany, the frequency and aetiology of dyspnoea will be investigated further in future studies. The dyspnoea observations with AZD6140 reported to date have not been clinically limiting and I look forward to further clinical evaluation of this promising antiplatelet agent during which there will be continued diligent monitoring of patient safety.

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