

Dyspnea and antiplatelet drugs: Little cause for concern with clopidogrel

Rickard E. Malmström, Paul Hjemdahl

Department of Medicine Solna, Clinical Pharmacology Unit, Karolinska Institutet and Karolinska University Hospital Solna, Stockholm, Sweden

Platelets play a central role in the pathophysiology of acute coronary syndromes (ACS), and dual antiplatelet therapy with aspirin and clopidogrel has resulted in significant treatment advances. However, important limitations exist among the current antiplatelet drugs, e.g. the large variability in individual responsiveness to platelet inhibition by clopidogrel, and several novel antiplatelet agents are in development. Two oral ADP (P2Y₁₂) receptor inhibiting drugs, the clopidogrel-like prodrug prasugrel and the directly acting competitive antagonist AZD6140, are currently investigated in late stage clinical trials for the treatment of ACS. At the doses chosen, both prasugrel and AZD6140 provide greater mean platelet inhibition than does clopidogrel at standard doses (1, 2). This will result in fewer “non-responders” to these antiplatelet drugs even though the inter-individual variability of response is still high and in the “clopidogrel-range” (1, 2). Data from the two phase 2 studies on AZD6140 (DISPERSE and DISPERSE-2) have revealed dyspnea as a dose-dependent side-effect with an incidence rate at 10.5% to 15.8%, respectively, in patients treated with AZD6140 at 90 mg and 180 mg twice daily (3, 4). For comparison, 6.4% of the patients treated with clopidogrel reported dyspnea in DISPERSE-2 (4). The association between antiplatelet drugs and dyspnea has been discussed before, but only anecdotal evidence for a causal relationship has been presented (see [5, 6]). With this background, it is of importance to determine whether currently used antiplatelet drugs, clopidogrel and aspirin, are associated with an increased incidence of dyspnea.

In the August issue of the Journal, Serebruany et al. (7) described the incidence of dyspnea, and analyzed likely causes of this symptom in patients treated with clopidogrel and aspirin. The authors have performed a thorough inventory in a large cohort of patients with questionnaires and interviews, and attempted to attribute symptoms to known causes of dyspnea in each individual case. In all, the incidence of dyspnea was 4.2%, most of which could be related to co-morbidities, e.g. chronic obstructive pulmonary disease and heart failure. Dyspnea of unknown aetiology among the clopidogrel treated patients was only 0.45% which supports the notion that dyspnea is not primarily caused by this drug.

The major limitations of the study are the observational design and the lack of a control (active or inactive) group. Evaluations of adverse effects of drug treatment are influenced by the methodology used to record them, and in observational studies there is always the possibility of confounding when attributing symptoms to co-existing treatment. In the absence of a control group, the incidence of dyspnea observed with this methodology in similar cohorts of patients not treated with clopidogrel is unknown. However, it is reassuring that dyspnea occurred at similarly low incidence rates with clopidogrel or aspirin treatment (4.5 and 4.7 %, respectively) in the CAPRIE study (7). Since no direct comparison between clopidogrel and AZD6140 was performed by Serebruany et al. (7), the study adds little to the questions surrounding the latter. The only reliable direct comparison between these two antiplatelet drugs, the DISPERSE-2 trial, indicated a higher dyspnea rate for AZD6140 than for clopidogrel (4). Substantially more data will accumulate from the comparison of the two drugs in the 18,000 patient PLATO study.

The results provided by Serebruany et al. (7) support the notion that clopidogrel treatment, at least at currently used doses, is not related to dyspnea. The mechanism behind the association between AZD6140 treatment and dyspnea (4) is still unknown. There remain several potential explanations. Dyspnea could be directly related to the level of P2Y₁₂ receptor antagonism (whether reversible or irreversible). If so, this side effect should be observed also with prasugrel which is being developed at dosages aimed at increasing its efficacy compared to clopidogrel (at currently used dosages). We have not found any such reports, however. On the other hand, if one does not search for a certain side-effect in clinical trials it can be easily overlooked, especially in a population in which the background level of the event sought after seems to be in the low to mid single digit percentage area (Serebruany et al. found plausible explanations for dyspnea in 9 out of 10 incident cases). Alternatively, dyspnea could be related specifically to AZD6140, and its pharmacodynamic properties. Of possible interest is that AZD6140 seems to dose-dependently increase uric acid levels (3, 4), but the mechanism for this has not been described. Elevated levels of the purine metabolite uric acid

Correspondence to:
Paul Hjemdahl
Department of Medicine Solna, Clinical Pharmacology Unit, Karolinska Institutet
Karolinska University Hospital Solna
SE-171 76, Stockholm, Sweden
Tel.: +46 (8) 5177 5293, Fax: +46 (8) 33 1343
E-mail: paul.hjemdahl@ki.se

Received August 25, 2008
Accepted August 25, 2008

Prepublished online September 5, 2008
doi:10.1160/TH08-08-0545

might reflect an increased bioavailability of endogenous adenosine, a substance known to provoke dyspnea. However, this remains entirely speculative. Large-scale phase 3 studies will provide further safety information on AZD6140 and reportedly additional studies will investigate the aetiology and clinical impact of dyspnea associated with AZD6140 treatment (6).

Patient safety is an important issue, and the mechanisms behind and implications of dyspnea during AZD6140 treatment will hopefully be clarified in time. Corresponding safety data for high-dose prasugrel treatment would be informative as well. Meanwhile, the present study supports the contention that there is little cause for concern with clopidogrel; this is important information regarding a widely used treatment.

References

1. Jernberg T, Payne CD, Winters KJ, et al. Prasugrel achieves greater inhibition of platelet aggregation and a lower rate of non-responders compared with clopidogrel in aspirin-treated patients with stable coronary artery disease. *Eur Heart J* 2006; 27: 1166–1173.
2. Storey RF, Husted S, Harrington RA, et al. Inhibition of platelet aggregation by AZD6140, a reversible oral P2Y₁₂ receptor antagonist, compared with clopidogrel in patients with acute coronary syndromes. *J Am Coll Cardiol* 2007; 50: 1852–1856.
3. Husted S, Emanuelsson H, Heptinstall S, et al. Pharmacodynamics, pharmacokinetics, and safety of the oral reversible P2Y₁₂ antagonist AZD6140 with aspirin in patients with atherosclerosis: a double-blind comparison to clopidogrel with aspirin. *Eur Heart J* 2006; 27: 1038–1047.
4. Cannon CP, Husted S, Harrington RA, et al. Safety, tolerability, and initial efficacy of AZD6140, the first reversible oral adenosine diphosphate receptor antagonist, compared with clopidogrel, in patients with non-ST-segment elevation acute coronary syndrome: primary results of the DISPERSE-2 trial. *J Am Coll Cardiol*. 2007; 50: 1844–1851.
5. Serebruany VL, Stebbing J, Atar D. Dyspnoea after antiplatelet agents: the AZD6140 controversy. *Int J Clin Pract* 2007; 61: 529–533.
6. Husted S, van Giezen JJJ. Dyspnoea and antiplatelet agents: revisited. *Int J Clin Pract* 2007; 61: 1590–1591.
7. Serebruany V, Pokov I, Kuliczowski W, et al. Incidence and causes of new-onset dyspnea in 3,179 patients treated with clopidogrel and aspirin combination after coronary stenting. *Thromb Haemost* 2008; 100: 314–318.