Journal of Cardiology Cases 6 (2012) e189–e190

Contents lists available at www.sciencedirect.com

Journal of Cardiology Cases

journal homepage: www.elsevier.com/locate/jccase

Editorial

Novel usage of sarpogrelate hydrochloride in patients with allergy-related variant angina

Variant angina pectoris is well known to be caused by reversible vasospasm on coronary artery. Indeed, although many variant angina patients have been diagnosed and treated worldwide, its precise mechanism remains to be elucidated. On the other hand, atherosclerosis-mediated structural stenosis on coronary artery could evoke angina attack on effort in patients with atherosclerotic angina. Therefore, it may be quite plausible that there are different mechanisms in the pathogenesis between effort angina and variant angina. So far, endothelial function has been reported to be impaired in patients with cardiovascular risk factors such as hypertension, dyslipidemia, diabetes mellitus, and smoking habit, leading to the onset and progression of atherosclerosis, which could subsequently result in cardiovascular events including coronary artery disease and cerebral stroke. In other words, endothelial dysfunction, viz. less release of nitric oxide from endothelium, could be usually and frequently found in patients with coronary artery disease. Similarly, endothelial dysfunction has been reported in patients with variant angina as well [1]. Rho-associated kinase (ROCK) has been shown as one of the critical target molecules to cause coronary vasospasm [2]. In vascular smooth muscle cells, ROCK mainly plays a critical role in vasoconstriction via modulation of Ca^{2+} sensitivity. In endothelial cells, ROCK has been also revealed to correlate with endothelial dysfunction [3]. Furthermore, ROCK activation has been reported to be clinically involved in patients with not only variant angina, but also effort angina [2]. Accordingly, endothelial dysfunction and increased ROCK activity in vasculature could play critical roles in both effort and variant angina. Nevertheless, the accurate difference of the mechanisms between effort angina and variant angina remains unclear.

Previously, the correlation between allergy and coronary vasospasm has been reported [4,5]. Sakata et al. have demonstrated a possible relationship of histamine with coronary vasospasm, i.e. the plasma concentration of histamine was elevated in patients with variant angina compared to that in control patients [6,7]. Histamine, released from mast cells and circulating basophils, is well known as one of the pivotal mediators for allergic diseases such as bronchial asthma and urticaria [8]. Indeed, it has been reported that mast cells in the adventitia of coronary artery are substantially related to coronary vasospasm, but to a lesser extent to coronary atherosclerosis [9]. Therefore, it appears to be quite possible that the release of histamine from mast cells located in coronary adventitia could evoke, at least in part, vasospasm in coronary arteries in patients with variant angina. Serotonin, similar to histamine, is also known to relate to bronchial asthma, an allergic disease. Indeed, Lechin et al. have shown that plasma serotonin levels were elevated in patients with asthma and the serotonin levels had a significant correlation with asthma severity [10]. Also, possible usage of serotonin receptor antagonists for asthma patients has been discussed [11]. However, the major source of serotonin in humans is platelets, which is different from histamine [8]. To date, a substantial relationship of variant angina with serotonin has not been elucidated. Interestingly, although a possible pathway of allergy-mediated vasospasm has been reported, it remains unknown whether allergy-mediated increases of histamine and/or serotonin could evoke endothelial dysfunction and/or increased ROCK activity (Fig. 1).

In this issue of the journal, a case report study demonstrated that the symptoms of refractory variant angina attack in the patient had a seasonal trend which is consistent with the allergy season evoked by *Dermatophagoides farina* [12]. Indeed, an allergic screening test revealed the presence of the patient's allergic reaction to *D. farina*. Of great interest, the additional administration of sarpogrelate hydrochloride, an antagonist of the 5-hydroxytryptamine subtype 2A (5-HT2A) receptor, improved the refractory angina attack completely. The 5-HT2A receptor belongs to the serotonin receptor family, namely the inhibition of variant angina attack could be mediated via blockage of serotonin-induced signals. Although sarpogrelate hydrochloride was administered in addition to other

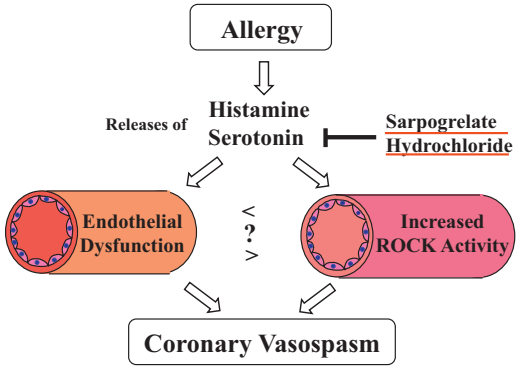

Fig. 1. A possible pathway of allergy-mediated coronary vasospasm. ROCK, Rho-associated kinase.

DOI of original article: http://dx.doi.org/10.1016/j.jccase.2012.07.010.

http://dx.doi.org/10.1016/j.jccase.2012.10.001

agents such as nicorandil, diltiazem, benidipine, nifedipine, and isosorbide dinitrate in the study, there might be other appropriate cases in which sarpogrelate hydrochloride should be administered not only as an additional agent, but also as a first- or second-choice agent. Taken together, a critical hint to determine the cases for the appropriate use of sarpogrelate hydrochloride has been suggested by Liu et al. Hence, sarpogrelate hydrochloride could be a novel and useful agent for the treatment of variant angina patients with seasonal trend attacks. Further studies are needed and awaited with great respect in order to convince the possible application of sarpogrelate hydrochloride to patients with variant angina.

Conflict of interest

There is no conflict of interest to report for the authors.

References

[1] Okumura K, Yasue H, Ishizaka H, Ogawa H, Fujii H, Yoshimura M. Endothelium-dependent dilator response to substance P in patients with coronary spastic angina. J Am Coll Cardiol 1992;20:838–44.
[2] Shimokawa H, Takeshita A. Rho-kinase is an important therapeutic target in cardiovascular medicine. Arterioscler Thromb Vasc Biol 2005;25:1767–75.
[3] Noma K, Kihara Y, Higashi Y. Striking crosstalk of ROCK signaling with endothelial function. J Cardiol 2012;60:1–6.
[4] Antonelli D, Koltun B, Barzilay J. Transient ST segment elevation during anaphylactic shock. Am Heart J 1984;108:1052–4.
[5] Bristow MR, Ginsburg R, Kantrowitz NE, Baim DS, Rosenbaum JT. Coronary spasm associated with urticaria: report of a case mimicking anaphylaxis. Clin Cardiol 1982;5:238–40.
[6] Sakata Y, Komamura K, Hirayama A, Nanto S, Kitakaze M, Hori M, Kodama K. Elevation of the plasma histamine concentration in the coronary circulation in patients with variant angina. Am J Cardiol 1996;77:1121–6.
[7] Okumura K, Yasue H, Matsuyama K, Matsuyama K, Morikami Y, Ogawa H, Obata K. Effect of H1 receptor stimulation on coronary artery diameter in patients with variant angina: comparison with effect of acetylcholine. J Am Coll Cardiol 1991;17:338–45.
[8] Barnes PJ. Histamine and serotonin. Pulm Pharmacol Ther 2001;14:329–39.
[9] Forman MB, Oates JA, Robertson D, Robertson RM, Roberts 2nd LJ, Virmani R. Increased adventitial mast cells in a patient with coronary spasm. N Engl J Med 1985;313:1138–41.
[10] Lechin F, van der Dijs B, Orozco B, Lechin M, Lechin AE. Increased levels of free serotonin in plasma of symptomatic asthmatic patients. Ann Allergy Asthma Immunol 1996;77:245–53.
[11] Cazzola I, Matera MG. 5-HT modifiers as a potential treatment of asthma. Trends Pharmacol Sci 2000;21:13–6.
[12] Liu F, Wada H, Sakakura K, Hirahara T, Arao K, Taniguchi Y, Ono D, Ako J, Momomura S. Refractory variant angina with a seasonal trend treated with sarpogrelate hydrochloride. JC Cases 2012:e1–2, http://dx.doi.org/10.1016/j.jccase.2012.07.010.

Kensuke Noma (MD, PhD)*
Department of Cardiovascular Regeneration and Medicine, Research Center for Radiation Genome Medicine, Research Institute for Radiation Biology and Medicine (RIRBM), Hiroshima University, 1-2-3 Kasumi, Minami-ku, Hiroshima 734-8551, Japan

Yasuki Kihara (MD, PhD, FJCC)
Department of Cardiovascular Medicine, Graduate School of Biomedical Sciences, Hiroshima University, 1-2-3 Kasumi, Minami-ku, Hiroshima 734-8551, Japan

Yukihito Higashi (MD, PhD)*
Department of Cardiovascular Regeneration and Medicine, Research Center for Radiation Genome Medicine, Research Institute for Radiation Biology and Medicine (RIRBM), Hiroshima University, 1-2-3 Kasumi, Minami-ku, Hiroshima 734-8551, Japan

* Corresponding authors. Tel.: +81 82 257 5831; fax: +81 82 257 5831.
E-mail addresses: knoma@hiroshima-u.ac.jp (K. Noma), yhigashi@hiroshima-u.ac.jp (Y. Higashi)

25 September 2012