New study cautions use of drugs to block 'niacin flush'

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Niacin, or vitamin B3, is the one approved drug that elevates "good" cholesterol (high density lipoprotein, HDL) while depressing "bad" cholesterol (low density lipoprotein , LDL), and has thereby attracted much attention from patients and physicians. Niacin keeps fat from breaking down, and so obstructs the availability of LDL building blocks.

Patients often stop taking niacin because it causes uncomfortable facial flushing, an effect caused by the release of a fat called prostaglandin or (PG)D2. PGD2 is the primary cause of the unwanted vasodilation, the "niacin flush." The dilation occurs when blood vessels widen from relaxed smooth muscle cells within vessel walls.

PGD2, formed by an enzyme called COX-2 and released by immune and skin cells, acts on a muscle cell-surface receptor called DP1 to cause the flushing. In fact, a combination of a DP1- blocking drug and niacin is being evaluated in a large clinical trial to determine its effectiveness in reducing heart attacks, as opposed to other drugs that reduce LDL cholesterol.

In work published in the Journal of Clinical Investigation this month, first authors Wenliang Song, MD, research assistant professor, and Jane Stubbe, PhD, postdoctoral fellow, in the Perelman School of Medicine, University of Pennsylvania, and their colleagues now question the wisdom of blocking DP1 in patients prone to cardiovascular disease, especially those taking niacin.

Drawing evidence from studies in mice and humans, they show that platelets -- complicated cells circulating in the bloodstream that stick together in the first phase of blood clotting -- make PGD2, which acts as a brake via DP1 on their own activation. This is surprising as PGD2 is made in platelets by COX-1, the target inhibited by low-dose aspirin.

COX-1 in platelets also makes thromboxane (Tx)A2, another fat that activates platelets. As low-dose aspirin is cardioprotective by thinning blood, the benefit from shutting down platelet TxA2 trumps the potential risk of suppressing platelet PGD2 production.

To gather more information on the potential risks from blocking DP1, the Penn investigators used mice lacking the DP1 receptor. However, unlike humans, mice do not express DP1 in their platelets. "Frankly, because of this, we did not expect to detect any signal of cardiovascular hazard in the mice," notes senior author Garret FitzGerald, MD, director of the Institute for Translational Medicine and Therapeutics.

However, deletion of DP1 made mice somewhat more susceptible to hardening of the arteries, the formation of aneurysm, thrombosis, and in some cases, high blood pressure. The researchers suggest that these findings are reflective of DP1 expression in vascular and immune cells in mice, just as in humans, despite its absence on mouse platelet cells.

Turning back to humans, the Penn investigators discovered that niacin evoked COX-1- dependent formation of both TxA2 and PGD2 in platelets and that a DP1 blockade enhanced the effect of TxA2 on platelet activation.

Taken together, these interwoven findings suggest that blocking the effects of PGD2 on DP1 is likely to be undesirable in patients with heart disease, and perhaps in particular, those taking niacin. That possibility is not addressed by the design of the large ongoing trial of the niacin/DP1

antagonist combination, say the researchers.

Should such a hazard exist, FitzGerald expects it to be confined to those patients not taking low-dose aspirin, along with niacin. "This potential hazard of blocking one aspect of PGD2 action, the one dependent on DP1, contrasts nicely with our recent report that blocking its other receptor, DP2, may be beneficial in limiting male-pattern baldness" said FitzGerald.

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