A Clinical Puzzle: Fibrates and Homocysteine Elevation

Editorial to: “Fibrates may cause an abnormal urinary betaine loss which is associated with elevations in plasma homocysteine” by M. Lever et al.

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Fibrates (gemfibrozil, bezafibrate, and fenofibrate) are commonly used drugs to treat patients with dyslipidemia, especially those with hypertriglyceridemia. A well-known effect of fibrate therapy is a significant increase in homocysteine levels which range from approximately 25% for gemfibrozil to up to 50% with fenofibrate or bezafibrate [1]. Severe elevation of homocysteine levels is associated with vascular and venous thrombosis and premature cardiovascular disease. A mild to moderate increase in homocysteine levels (> 15 mg/dl) is also a risk marker for coronary heart disease [2] but numerous clinical trials to reduce homocysteine by folic acid supplementation have not shown a clinical benefit [3]. Therefore, the clinical relevance of the homocysteine increase with fibrate therapy has been uncertain. Recent clinical trial evidence has raised concerns that this effect may potentially offset some of the beneficial lipoprotein changes and negate much of the cardiovascular benefits of fibrate treatment [4]. In the FIELD trial, fenofibrate therapy did not achieve a significant benefit over placebo in the primary endpoint

(fatal and non-fatal MI) but did reduce total cardiovascular events (-11% $p<.05$) [5]. However, there was an increase in venous thrombosis and pulmonary embolism with fenofibrate treatment that was postulated to potentially be due to the 50% increase in homocysteine [5]. In the FIELD trial there was an inverse correlation between baseline homocysteine levels and HDL-C or ApoA1 in the placebo and fenofibrate groups [6]. The greater the increase in homocysteine induced by fenofibrate, the smaller the increases in HDL-C and ApoA1 ($p<.0001$ for linear trends). On the other hand, there was highly significant and positive relationship between fenofibrate-induced changes in homocysteine and ApoAII levels. Presently, although the fibrate-induced increase in homocysteine is worrisome, there are no recommendations to measure homocysteine or modify dose of treatment with fibrates due to this side effect.

Lever and colleagues, in this issue, report that betaine excretion is increased with bezafibrate therapy [7]. Betaine is a major osmolyte responsible for cell volume regulation but also is a source of methyl groups for the regeneration of S-adenosylmethionine, thereby sparing the consumption of homocysteine. In a relatively small patient cohort in a lipid clinic ($n=32$), Lever and colleagues found that abnormal betaine excretion is common in patients on bezafibrate therapy. Although this study is too small to make definitive conclusions, it suggests an important hypothesis that may improve fibrate therapy or assist in the development of novel PPAR- α agents that do not increase homocysteine levels.

Over the past few years, several investigators have advocated folic acid, B12, and B6 supplementation with fibrate therapy to obviate the induced increase in homocysteine. In a double-blind cross over study, 650 mcg of

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folic acid, 50 mcg of vitamin B12, and 5 mg of B6 abolished the 44% increase in homocysteine with fenofibrate treatment [8]. In another small clinical trial, folic acid alone ameliorated the rise in homocysteine with 200 mg/day of micronized fenofibrate [9].

Betaine supplementation has also been shown to reduce plasma homocysteine and reduce the increase in homocysteine after methionine loading by 50% [10]. The combination of betaine and folic acid together may provide substantial decreases in homocysteine levels. Betaine also attenuates atherosclerosis in ApoE knockout mice [11]. Therefore, based on the findings of Lever and colleagues, there is an intriguing recommendation to consider betaine supplementation for patients on fibrate treatment. Perhaps a combination of folic acid and betaine would provide enhanced benefits for patients on fibrate therapy.

Metabolic syndrome is associated with higher homocysteine levels, and fibrates are frequently utilized to affect the mixed dyslipidemia in this growing patient population [12]. The concerns raised by the FIELD trial have spotlighted the adverse effect of fibrates on homocysteine metabolism. If betaine or a combination of betaine and folic acid can modify this adverse effect, then this will potentially lead to improved patient outcomes. The upcoming ACCORD trial results that evaluated the effects of fenofibrate in combination with a statin vs statin alone will provide valuable insights into the benefits of fibrate-statin combination on CVD outcomes in patients with high-risk diabetes. If this study demonstrates no significant CVD protection with fenofibrate, then fenofibrate will potentially require another clinical evaluation in combination with betaine supplementation, especially if a subgroup of patients with higher homocysteine levels have lower HDL-C levels.

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