Homocysteine Elevation with Fibrates: Is It a Class Effect?

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Abstract

Background: Case-control and prospective studies indicate that an elevated plasma homocysteine level is a powerful risk factor for atherosclerotic vascular diseases. Certain medications can induce hyperhomocystinemia, such as methotrexate, trimethoprim and anti-epileptic drugs. There are few reports indicating an interaction between lipid-lowering drugs (cholestyramine and niacin) and homocysteine. Recently, an interaction was shown between fenofibrate and benzafibrates (a fibric acid derivative) and homocysteine plasma levels.

Objectives: To evaluate the effects of different fibrates on plasma homocysteine levels and to measure the reversibility of this effect

Methods and Results: We investigated the effects of ciprofibrate and bezafibrate on homocysteine levels in patients with type IV hyperlipidemia and/or low high density lipoprotein levels. While a 57% increase in homocysteine was detected in the ciprofibrate-treated group (n = 26), a 17% reduction in homocysteine was detected in the group treated with bezafibrate (n = 12). The increase in homocysteine in the ciprofibrate-treated group was sustained for the 12 weeks of treatment and was partially reversible after 6 weeks of discontinuing the ciprofibrate therapy.

Conclusions: These results indicate that an increase in plasma homocysteine levels following administration of fibrates is not a class effect, at least in its magnitude. Moreover, it is reversible upon discontinuation of the treatment.

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Case-control and prospective studies indicate that an elevated plasma homocysteine level is a powerful risk factor for atherosclerotic vascular disease [1], with increased risk for coronary heart disease [2,3] and stroke [4,5]. Certain medications can induce hyperhomocystinemia, especially those affecting the vitamins related to homocysteine (folate, vitamin B12 and vitamin B6) such as methotrexate [6], trimethoprim [7] and anti-epileptic drugs [8]. There are few lines of evidence suggesting interaction between lipid-lowering drugs (cholestyramine and niacin) and homocysteine [9,10].

de Lorgeril et al. [11] and Dierkes et al. [12] recently reported an increase in plasma homocysteine of 46% and 44% respectively, in patients treated with fenofibrate for 12 weeks. However, the authors did not evaluate the reversibility of this potentially harmful side effect. Dierkes et al. [12] reported that bezafibrate treatment also increases plasma homocysteine levels although to a lesser degree, i.e., 17%. Although clinical and angiographic trials have shown that fibrates reduce atherosclerotic complications and progression [13–18], increased plasma homocyteine due to fibrates may indicate a class side effect that may be potentially harmful. In the present study we investigated the effect of cipofibrate and bezafibrate on plasma homocysteine levels and the reversibility of this side effect.

Materials and Methods

The study was approved by the Ethical Review Committee of the Sheba Medical Center, and was in accordance with its guidelines.

Patients

Twenty-six patients with or without a previous history of coronary heart disease with type IV dislipidemia (triglycerides above 250 mg/dl and below 400 mg/dl) or low HDL (HDL < 35 mg/dl) were recruited to the study. Patients with diabetes, abnormal liver or kidney function, unstable angina pectoris, or myocardial infarction in the last 6 months, or patients on active hypolipidemic therapy were excluded.

Study design

The study was designed for 28 weeks in two phases [Figure 1]:

- *Phase A (n = 26)*. After giving informed consent, patients were instructed to follow a low fat low carbohydrate diet for 4 weeks. Eligible patients then received ciprofibrate 100 mg per day for 12 weeks (n = 26). Homocysteine levels, lipid profile, liver function tests and creatine phosphokinase levels

HDL = high density lipoprotein

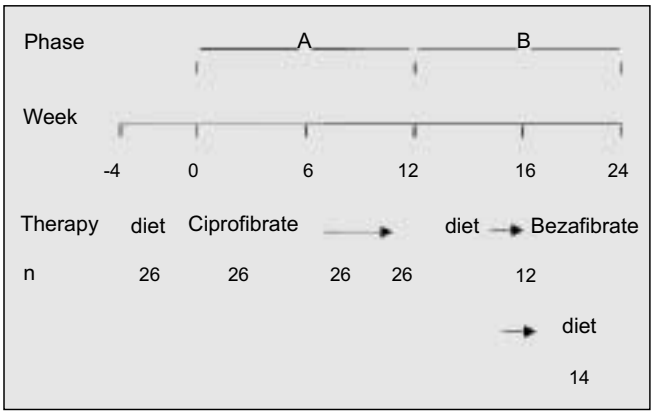

Figure 1. Study design – In phase A, 26 patients were treated with cipofibrate 100 mg daily (for 12 weeks). In phase B, after washout of 6 weeks (weeks 12–18) 12 patients received bezafibrate 400 mg daily.

were measured at baseline and after 6 and 12 weeks of therapy.

- *Phase B (n=12)*. After 6 weeks withdrawal from ciprofibrate, plasma homocysteine and lipid levels were measured. Patients with triglyceride levels above 250 mg/dl received bezafibrate 400 mg in slow-release formulation for another 6 weeks. Blood tests were taken before and after bezafibrate treatment. The patients with triglyceride levels below 250 mg/dl were given a low cholesterol low fat diet.

Homocysteine determination

Blood samples from patients after a 12 hour fast were collected into tubes containing EDTA. The plasma, kept on ice, was obtained immediately by centrifugation at 4°C and stored at –20°C. Total plasma homocysteine was determined by high performance liquid chromatography with a fluorescence detection based on a method described previously by Jacobsen et al. [19] as modified by Pastore et al. [20]. The derivatized samples were injected onto a Shandon Hypersil-BDS Elite 250x4.6 column installed in a Merck-Hitachi HPLC system with L7100 pump, L7250 autosampler and L7480 fluorimetric detector.

Statistical analysis

All values are reported as mean ± SE. Statistical analyses were done by one-way repeated measures analysis of variance and Student-Newman-Keuls methods.

Results

Twenty-six eligible patients who met the inclusion criteria were enrolled in phase A. There were 22 men (84%) and 4 women (26%) with an average age of 53 (35–59 years). The average body mass index was 28.1 (± 4.3), range 21.5–37.4 at the start of the study and did not change significantly during the study. Four of the patients were smokers (15%) and 8 (39%) had a history of CHD.

CHD = coronary heart disease

Twelve patients who met the inclusion criteria after ciprofibrate withdrawal took part in phase B of the study (the other 15 patients had normal lipid levels at week 18 and therefore were excluded from phase B).

Lipid profile

The triglycerides level was 392.2±34.4 at baseline, which declined to 229.4±16.8 and 236.9±21.3 mg/dl after 6 and 12 weeks of ciprofibrate treatment, a reduction of 41% and 39% respectively. After 6 weeks withdrawal from ciprofibrate, triglyceride levels measured 360.3±37.1 mg/dl in the 12 patients enrolling in phase B, and declined after 6 weeks of bezafibrate treatment to 242.9±37.3 mg/dl, a reduction of 42% [Table 1]. Triglyceride levels were 212 ±22.2 and 296.1±31.2 mg/dl at 18 and 24 weeks respectively in the 14 patients on low cholesterol low fat diet alone in phase two.

HDL levels were 25.5±1.5 mg/dl at baseline and rose to 35.6±1.4 and 35.9±1.9 mg/dl after 6 and 12 weeks of ciprofibrate treatment, an elevation of 39% and 40% respectively. After 6 weeks withdrawal from ciprofibrate, HDL declined to 29.5±2.5 mg/dl and rose after 6 weeks of bezafibrate treatment to 34.3±3.0 mg/dl, an elevation of 30% (in the 12 patients enrolling to phase B) [Table 1]. HDL levels measured 32.4±1.8 and 29.8±2.1 mg/dl at 18 and 24 weeks respectively in the 14 patients on low cholesterol low fat diet alone in phase two.

Plasma homocysteine levels

- *Phase A*. The average homocysteine level at enrollment was 6.80±0.36 nmol/ml and inreased to 10.72±1.05 and 10.60±0.84 nmol/ml after 6 and 12 weeks of ciprofibrate treatment (57% and 53% elevation respectively) ($P < 0.0001$). In only three patients were homocysteine levels lower after treatment. In five participants the homocysteine level more than doubled [Figure 2A].
- *Phase B*. The average homocysteine levels in the 12 patients who completed phase A and B were 6.93±0.62 nmol/ml at baseline, and 10.65±1.21 and 11.7±1.35 nmol/ml after 6 and 12 weeks of ciprofibrate treatment respectively. These

Table 1. Triglycerides and HDL plasma levels

	Phase A			Phase B	
Week	0	6	12	18	24
n	26	26	26	11	11
TG mean	392.2	229.4	236.9	360.3	242.9
SD	34.4	16.8	21.3	37.1	37.3
% change	100.0	58.5	60.4	100.0	67.4
HDL mean	25.5	35.6	35.9	29.5	34.3
SD	1.5	1.4	1.9	2.5	3.0
% change	100.0	139.7	141.1	100.0	116.4

Triglycerides (TG) and HDL levels during phase A treatment with cyprofibrate (weeks 6 and 12) and phase B washout period (week 18) and treatment with bezafibrate (week 24).

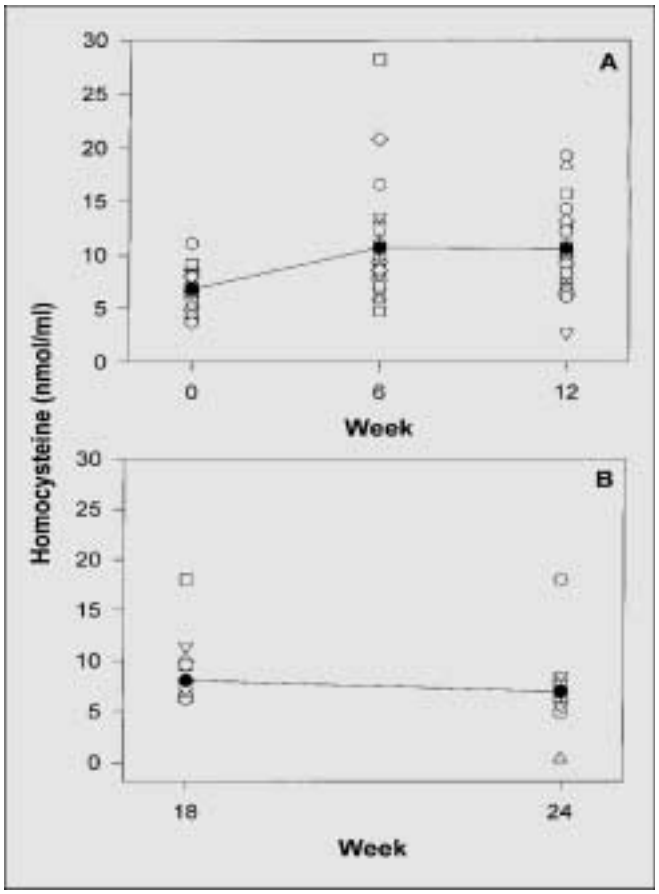

Figure 2. Plasma homocysteine levels in patients receiving ciprofibrate [A] and bezafibrate [B]. Week 0: before treatment; weeks 6 and 12: 100 mg daily ciprofibrate; week 18: (6 weeks washout); and week 24: 400 mg bezafibrate daily. $P < 0.0001$ (week 6 vs. 0 week, 12 vs. 0) $P = 0.22$ (week 18 vs. 24).

levels are not significantly different from those in the other 14 subjects who did not participate in phase B.

The average homocysteine level after 6 weeks withdrawal from ciprofibrate was 8.23 ± 0.67 nmol/ml (week 18). After 6 weeks of bezafibrate treatment homocysteine level was 6.83 ± 0.41 nmol/ml (week 24), a reduction of 17%, not significant ($P = 0.22$) [Figure 2B]. The homocysteine levels were 8.25 ± 0.72 and 8.02 ± 0.73 nmol/ml at 18 and 24 weeks respectively in the 14 patients on a low cholesterol low fat diet alone in phase two.

Discussion

In this study we showed a significant (53–57%) and sustained increase in plasma homocysteine levels in patients treated with ciprofibrate. Twelve of these patients whose response was a 65% increase with ciprofibrate showed a 17% reduction in their plasma homocysteine levels when treated with bezafibrate.

Fibrates are currently recommended as first-line drugs for the treatment of hypertriglyceridemia. It was recently found that the pharmacological effects of fibrates are mediated through an alteration in transcription genes encoding for proteins that control lipoprotein metabolism (PPARs) [21–24]. Although an association between homocysteine and PPARs-delta has been suggested [25], no such association has been shown for PPAR-alpha.

Clinical trials and angiographic studies have shown a reduction in both CHD mortality and atheroma progression with fibrates treatment, however except for the HDL Intervential Trial [18] most of them have failed to show a reduction in overall mortality [13–17]. Intervention trials with first- and second-generation fibrates, namely clofibrate in the Cooperative Trial on Primary Prevention of Ischemic Heart Disease [13], and gemfibrozil in the Helsinki Heart Study [14], showed a reduction in coronary mortality but no difference in total death rate. Ciprofibrate and bezafibrate are second-generation fibrates. In a recent comparative study, ciprofibrate produced a greater decrease in triglycerides than did bezafibrate, although both had a similar effect on HDL [15].

Trials with bezafibrate as a hypolipidemic drug in patients surviving myocardial infarction are contradictory. The BCAIT trial [16] showed that CHD progression and coronary event could be reduced after 5 years with bezafibrate treatment. The Bezafibrate Interaction Prevention (BIP) Registry study [17], conducted in Israel, failed to show a significant reduction in overall mortality and sudden death after 6.2 years of bezafibrate treatment. On the other hand, in a recent study by Rubins and colleagaues [18], gemfibrozil significantly reduced the risk for major cardiovascular events but, even in this study, there was no significant effect on total mortality [17]. One explanation for the borderline effect of fibrates on CAD mortality in some studies may be an insignificant effect of the dislipidemia that they correct, i.e., hypertriglyceridemia and/or low HDL. Another explanation might be the effects of fibrates on other risk factors, increasing the risk for CHD.

Case-control and prospective studies indicate that an elevated plasma homocysteine level is a powerful risk factor for atherosclerotic vascular disease [1], with an increase in the risk of coronary heart disease [2,3] and stroke [4,5]. Certain drugs can induce hyperhomocystinemia, especially those affecting the vitamins related to homocysteine (folate, vitamin B12 and vitamin B6) such as methotrexate [6], trimethoprim [7] and anti-epileptic drugs [8].

In the current study, ciprofibrate and bezafibrate were given subsequently to type IV hyperlipidemic patients with high triglycerides level and/or low HDL. The effect on the lipid profile was similar with ciprofibrate and bezafibrate following 6 weeks of treatment. In phase A of the study, a 57% average elevation of homocysteine levels was noted in 26 patients after 6 weeks of ciprofibrate treatment. The high level remained unchanged after a further 6 weeks. These results are similar to the reported results with fenofibrates [11,12]. In phase B on the other hand, although not significant, there was a 17% insignificant decrease in homocysteine in 12 patients after 6 weeks of bezafibrate treatment. Although only 12 of the 26 patients proceeded to phase B (the others were excluded due to triglyceride levels below 250 mg/dl at week 18), this should not

create a significant bias as they were not different from the entire group in their response to ciprofibrate in phase A and each of them served as a control of him or herself. Moreover, the 14 patients not treated with bezafibrate had stable homocysteine levels at week 18 and 24, whereas the 12 treated with bezafibrates lowered their homocysteine levels by 17%. The difference in the response to ciprofibrate and benzafibrates with regard to homocyteine levels cannot be attributed to genetic background (i.e., mutation to MTHFR, etc.) as each subject served as his or her own control in phase A and B.

Our results contradict those of Dierkes et al. [12], who report a 17% increase in plasma homocysteine levels with bezafibrate. This discrepancy can be explained by the relatively small groups of patients in both studies. The fact that the 12 patients in our study served as their own control (phase A ciprofibrate and phase B bezafibrate) suggests that this is not a class effect, at least in its magnitude.

De Lorgeril et al. [11] and Dierkes et al. [12] did not evaluate the reversibility of this potentially harmful side effect in their studies. We followed the homocysteine levels 6 weeks after discontinuing ciprofibrate. In all patients homocysteine levels declined, although not to baseline. A longer follow-up might be needed. The unequivocal results of some of the large clinical trials with fibrates [13–18] may be attributed to the influence of fibrates on homocysteine and/or other metabolic pathways. Whether the increase of homocysteine outweighs the benefit of ciprofibrate on lipid profile and fibrinogen needs to be assessed. Further studies are needed to investigate at which step of the metabolic pathway the alteration occurs, what the difference is between the effect of various fibrates, and whether those unfavorable changes can be corrected with vitamin supplementation.

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