Clinical Notes

Fenofibrate therapy to lower serum triglyceride concentrations in persons with spinal cord injury: A preliminary analysis of its safety profile

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Context: Fenofibrate is used to treat elevated serum triglyceride (TG) concentrations (e.g. ≥150 mg/dl). The lipoprotein profile of most individuals with spinal cord injury (SCI) would not satisfy conventional criteria to initiate lipid-lowering therapies. Serum TG concentrations of 115 and 137 mg/dl were recently identified as potential intervention thresholds for persons with a SCI proximal to the 4th and below the 5th thoracic vertebrae, respectively. Fenofibrate therapy has not been tested for safety in persons with SCI.

Methods: An open-label trial was performed in 15 persons with SCI to determine the safety profile of 4 months of once-daily fenofibrate (145 mg tablet) treatment when initiated using modified intervention thresholds. Fasting blood tests and a review of systems were performed monthly to determine changes in liver and kidney function, as well as overall health status.

Results: Fifteen subjects participated and 4 had an adverse event (e.g. 2 with gastrointestinal distress; 2 with elevated liver enzymes). Three subjects discontinued the trial within the first month and one participant remained in the trial with no further adverse events. Two participants were discontinued from fenofibrate after 2 months after not responding to treatment, as per protocol, and 10 participants completed the 4-month trial without experiencing an adverse event.

Conclusion: In persons with SCI, 4 months of fenofibrate therapy initiated at lower threshold serum TG concentrations did not result in an increased incidence of adverse events compared to that reported in the general population. Fenofibrate therapy appears to be well tolerated in persons with SCI.

Keywords: Lipids, Lipoproteins, Quadriplegia, Paraplegia, Cardiovascular diseases

Context

There are numerous medications approved by the Food and Drug Administration to treat dyslipidemia. Depending on the serum concentration of the abnormal lipid constituent [i.e. high- and low-density lipoprotein

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cholesterol (HDL-C, LDL-C, respectively), triglycerides (TG)], the magnitude of deviation from a clinically-acceptable range, co-morbidities, and/or contraindications to treatment, one or more agents from several classes of lipid regulators may be prescribed including HMG CoA reductase inhibitors (i.e. statins), bile acid sequestrants, nicotinic acid, and fibric acid derivatives (i.e. fenofibrate).[1] Statins have proven efficacy to lower elevated serum LDL-C, but this class of agents only has modest effects on modifying the serum HDL-C or TG concentrations,[1,2] except in those with hypertriglyceridemia (e.g. $\geq$250 mg/dl).[3–6] In appreciation of the characteristics that contribute to dyslipidemia in the majority of persons with spinal cord injury (SCI),[7–11] statins may not be the appropriate first line agent because the serum HDL-C concentrations are markedly depressed and the serum TG concentrations are in the normal range, or slightly elevated[8,12–20] despite observations of equivalent or increased risk of cardiovascular mortality.[21–24]

It was previously demonstrated in persons with chronic, non-ambulatory SCI that functional sympathetic nervous system (SNS) innervation to the liver and abdominal viscera had a significant influence on the circulating concentrations of TG-rich lipoproteins.[25] Despite similar visceral abdominal adipose tissue volume and degrees of insulin resistance, individuals with a neurological level of SCI at or proximal to the 4th thoracic vertebrae (↑T4) had significantly lower TG concentrations than individuals with an injury at or distal to the 5th thoracic vertebrae (↓T5),[25] the initial site for preganglionic projections from the spinal cord to the celiac and superior mesenteric ganglion that innervate the abdominal viscera.[26,27] Thus, it was speculated that the "normal" serum TG concentrations in persons with SCI do not adequately convey the risk for cardiovascular disease (CVD) when applying screening paradigms that have proven efficacy in the general population.[28] In a recent retrospective report, the relationship between circulating TG and HDL-C concentrations were explored to determine if a different threshold value for abnormal serum TG concentrations was present/needed in SCI cohorts that are assumed to have functionally impaired (↑T4) or spared (↓T5) SNS innervation to the liver and other abdominal tissues.[29] More specifically, the serum TG concentrations at which serum HDL-C equals 40 mg/dl, a concentration below which is an independent risk factor for coronary artery disease (CAD),[30] was determined in 223 persons with SCI ↑T4 and 178 with ↓T5. The analyses revealed that the serum TG threshold was lower in SCI ↑T4 (e.g. 115 mg/dl) than able-bodied controls (e.g. 137 mg/dl) or that of the SCI ↓T5 group (e.g. 137 mg/dl), suggesting that persons with higher cord lesions have a lower serum TG concentration associated with increased CAD risk. Therefore, an opportunity exists for these individuals to benefit from a pharmacological intervention to reduce elevated serum TG concentrations.

Fenofibrate, a fibric acid derivative, binds to peroxisome proliferator-activated receptor α (PPAR-α) to mobilize fatty acids and enhance lipid metabolism.[31] PPAR-α is a ligand-activated transcriptional factor that binds to a DNA sequence, the peroxisome proliferator response element, on the promoter region of a target gene.[32] PPAR-α is expressed in tissues where mitochondrial and peroxisomal fatty acid β-oxidation rates are relatively high.[33,34] Metabolism of TG-rich lipoproteins are strongly affected by activation of PPAR-α agonists,[31] which induce enzymes associated with β-oxidation in the liver, shifting free fatty acid metabolism from TG synthesis to that of catabolism, thereby reducing the number of TG-rich lipoprotein particles that are produced and secreted into the circulation.[35] PPAR-α agonists increase the activity of lipoprotein lipase, which serves to reduce serum TG concentrations.[36,37] Thus, the use of PPAR-α agonists provides a dual therapeutic approach of reducing TG production in the liver and by removing TG from the circulation.

HDL-C metabolism is also favorably influenced by treatment with PPAR-α agonists by modulating steps in the reverse cholesterol transport, a process by which HDL particles facilitate the uptake of cholesterol from the periphery for return to the liver, where cholesterol is removed from the HDL particle and secreted into bile as a bile salt.[36] PPAR-α agonists also contribute to the upregulation of apolipoprotein A-I and AII synthesis in the liver,[38,39] which are the apolipoproteins in HDL particles. The enhanced hydrolysis and removal of TG from the circulation by PPAR-α agonists permit the HDL particle to increase in size, which is believed to facilitate its anti-atherogenic potential. Individuals who have elevated serum TG-rich lipoproteins and low HDL-C may obtain therapeutic benefit by treatment with PPAR-α agonists. For these reasons, PPAR-α agonists are often the first line agent for 31% of the adult US population who have serum TG concentrations $>$150 mg/dl.[1,40]

Evidence for the therapeutic efficacy of fibric acid derivatives including fenofibrate is widely available.[41–55] Fibric acid derivatives promote favorable changes to the serum levels of TG (41–53% decrease), LDL-C (6–20% decrease) and HDL-C (5–20% increase) in various clinical trials of varied durations and clinical endpoints in

persons with hypertriglyceridemia.[49–50] However, there is controversy in the general population concerning the benefit of lowering the serum TG concentration, despite several randomized clinical trials that have shown a modest benefit with regard to CVD endpoints (e.g. myocardial infarction, stroke, sudden cardiac death) but with no benefit observed for overall mortality rates.[51] After initiating fenofibrate treatment, the peak therapeutic changes are observed within 2 weeks for serum TG, 4 weeks for serum LDL-C and 12–16 weeks for serum HDL-C.[49] The clinical recommendation is that individuals who are refractory to treatment (e.g. non-responders), as determined by the absence of a ≥25% reduction in the serum TG concentration after 2 months of monotherapy, should have the medication discontinued. In addition to the potential lack of therapeutic efficacy, individuals on fibric acid derivatives may experience a range of abnormal signs and symptoms, including, but not limited to, elevated liver enzymes (3–13% incidence rate), gastrointestinal (GI) distress (e.g. constipation, diarrhea, abdominal pain, and/or nausea; ~5% incidence rate), and skin rash.[56,57] The purpose of this manuscript was to report the adverse event profile that occurred during a 4-month open-label treatment trial with fenofibrate in a sample of persons with SCI.

Methods

A prospective, open-label safety and efficacy trial of fenofibrate monotherapy was performed in 15 persons with chronic SCI to determine if treatment reduced the serum TG concentrations and that therapy did not result in a greater incidence, variety, or severity of side effects compared to those observed in the general population. Because of the numerous outcomes of this trial, the findings of safety and efficacy for fenofibrate administration in persons with SCI are being reported separately. To be considered for study enrollment, subjects must have met the inclusion criteria [e.g. male or female between the ages of 21 and 69 with American Spinal Injury Association Impairment Scale designation of A, B, or C][58] and exclusion criteria [e.g. be free of acute illness or infection; have reduced glomerular filtration rate (e.g. eGFR <60 ml/min) or liver function tests (LFTs ≥2.5 times greater than the upper limit of normal); current pharmacological treatment with agents known to effect the serum TG concentration; hypersensitivity to fenofibrate; existing CAD, congestive heart failure, or recent history of myocardial infarction (i.e. ≤12 months); pregnancy or women who may become pregnant during the course of the study, or those who are nursing; have diminished mental capacity; or an inability or unwillingness of subject to provide informed consent].

A screening visit was performed on 70 persons with SCI to identify subjects with elevated serum TG concentrations (i.e. paraplegia: ≥135 mg/dl; tetraplegia ≥115 mg/dl)[29] after a ≥12-hour overnight fast. Fifteen participants were identified as having elevated serum TG values and received once-daily fenofibrate therapy (145 mg tablet; Tricor®, AbbVie Inc., North Chicago, IL, USA) (Table 1). The clinically acceptable time point in deciding whether to withdraw or continue fenofibrate treatment is 2-months and is based on whether there was a ≥25% reduction in the serum TG concentration; in the absence of an improvement, drug therapy was discontinued. For those who responded to fenofibrate therapy (e.g. a reduction of serum TG ≥25%), treatment was continued for an additional 2 months in the trial. At baseline and then at each month thereafter, a review of systems was obtained to identify any deviation from baseline status and venous blood collection was performed between 8 am and noon after an overnight fast. The blood specimen were sent to a commercial laboratory (LabCorp, Raritan, NJ, USA) for evaluation of liver function tests (LFTs), kidney function (i.e. estimated glomerular filtration rate), and a complete blood count with differential.

Results

The characteristics of the 15 participants treated with fenofibrate are provided (Table 1), and participants had a baseline serum TG concentration of 204 ± 60 mg/dL. Four of the 15 participants experienced an adverse event (e.g. 2 had abnormal bowel patterns and 2 had elevated LFTs) and the event was significant enough for 3 subjects to discontinue the medication. Two participants reported experiencing GI discomfort, constipation or a change in the consistency of the stool

Table 1 Characteristics of treatment participants.

n	15
Age (years)	51.3 ± 13.0
Height (m)	1.76 ± 0.10
Weight (kg)	94.4 ± 26.7
BMI (kg/m^2)	30.2 ± 6.6
DOI (years)	19.4 ± 12.8
Gender (M / F)	12/3
Paraplegia/Tetraplegia (n)	10/5
AIS (A/B/C)	8/3/4
Ethnicity (AA/Hisp/White)	2/6/7

Data are presented as group mean ± SD. Abbreviations: AA, African American; AIS, American Spinal Injury Association Impairment Scale; BMI, body mass index; DOI, duration of injury; F, female; Hisp, Hispanic; M, male.

Table 2 Serum concentration of safety labs at each visit.

n	Normal Range	Baseline 15	Month 1 14	Month 2 12	Month 3 10	Month 4 10
eGFR	>59	119 (108, 130)	114 (103, 124)	111 (101, 120)	112 (101, 120)	115 (100, 131)
ALT	0–32 IU/L	23 (18, 27)	42 (17, 67)	34 (22, 46)	33 (19, 46)	32 (19, 45)
AST	0–40 IU/L	22 (9, 24)	32 (19, 45)	29 (20, 37)	25 (20, 30)	28 (21, 36)
GGT	0–60 IU/L	27 (19, 35)	43 (13, 74)	33 (17, 50)	33 (19, 48)	22 (14, 30)
RBC	3.77–5.28 g/dL	4.73 (4.47, 4.99)	4.71 (4.46, 4.95)	4.62 (4.35, 4.90)	4.62 (4.28, 4.96)	4.53 (4.22, 4.84)
WBC	3.4–10.8 × $10e^3$/uL	6.7 (6.0, 7.5)	6.0 (5.2, 6.9)	7.0 (5.5, 8.6)	6.3 (4.7, 7.8)	6.0 (4.2, 7.7)
MCV	79–97 fL	86 (84, 89)	87 (85, 89)	87 (85, 90)	87 (84, 90)	87 (84, 89)
MCH	26.6–33.0 pg	29.3 (28.4, 30.1)	29.1 (28.1, 30.0)	29.3 (28.3, 30.2)	28.9 (28.0, 29.8)	29.3 (28.4, 30.2)
MCHC	31.5–35.7 g/dL	33.9 (33.3, 34.4)	33.4 (33.0, 33.8)	31.0 (25.4, 36.5)	32.8 (31.7, 33.9)	33.8 (33.2, 34.3)
RDW	12.3–15.4%	14.2 (13.8, 14.5)	14.3 (13.9, 14.7)	14.3 (13.8, 14.9)	14.3 (13.8, 15.0)	14.8 (14.0, 15.5)

Data are express as group mean (95% CI). eGFR, estimated glomerular filtration rate: ALT, alanine aminotransferase; AST, aspartate aminotransferase; GGT, gamma-glutamyl transferase; RBC, red blood cell; WBC, white blood cell; MCV, mean corpuscular volume; MCH, mean corpuscular hemoglobin; MCHC, mean corpuscular hemoglobin concentration; RDW, red cell distribution width.

that began shortly after initiating drug treatment or after a few weeks of use and each requested to withdraw from the study. One participant had elevated LFTs at Month 1, which is reflected in the group mean LFT values that exceeded the upper limit of normal (Table 2). This participant was terminated from the study in accordance with the exclusion criterion for elevated LFTs (e.g. ≥2.5 times greater than the upper limit of normal) after a second blood test confirmed the elevated ALT (~4 times greater than the upper limit of normal). ALT and GGT values were also found to be elevated (>2.5 times greater than the upper limit of normal) in a separate participant at the Month 2 visit; however, the participant reported consuming a number of alcoholic beverages while at a party the night prior to the study visit. Repeat LFTs performed a few days later revealed that values had returned to below the threshold for study termination. After consultation with the participant's primary care physician, who was not a member of the study team, and the Institutional Review Board, the participant was deemed safe to remain in the study. All 3 participants who discontinued treatment had a prompt resolution of the adverse event and the 4th participant had no further issues and successfully completed the 4-month trial. Beyond these 2 adverse event types (e.g. abnormal bowel patterns, elevated LFTs), there were no other signs or symptoms attributable to the drug therapy in any participants for the entire 4-month treatment trial (Table 2).

Conclusion

Once-daily fenofibrate monotherapy in persons with SCI, administered at a lower serum TG concentration than that which conventionally triggers treatment, does not appear to increase the incidence, severity, or variety of adverse side effects known to occur with fenofibrate treatment in the general population.[56,57] The expected incidence rate for constipation with fenofibrate use is ~2% in the general population when the medication is prescribed to treat TG concentrations at higher threshold values.[56,57] Constipation has been reported to occur in up to 39% of persons with SCI.[59] Because of the well appreciated prevalence of bowel dysfunction in persons with SCI, and the observation that constipation was present in 2/15 participants (~13%) in our trial, further evaluation on the effect(s) of fenofibrate treatment on bowel function is necessary. The occurrence of constipation in our trial with drug treatment was well below that which may be expected to occur in persons with SCI, but above the reported rate of non-SCI persons on fenofibrate therapy. From this safety analysis, fenofibrate monotherapy appears to be tolerated in persons with SCI as evidenced from the relatively low incidence of expected adverse events compared to the wider range of adverse event that have been reported to occur in the general population.[56,57] The authors acknowledge that a larger clinical trial in the SCI population is required to confirm the findings of this preliminary study and definitively determine the type, frequency, and severity of adverse events, including a more comprehensive evaluation of bowel function that may occur with longer duration of treatment with fenofibrate.

Disclaimer statements

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