Statin Intolerance in a Patient with Gilberts Syndrome and Hypercholesterolemia

Authors

I. Jialal, D. Siegel

Affiliation

VA Medical Center, Mather and UC Davis Medical Center, Sacramento

Key words

- LDL
- cardiovascular risk management
- coronary artery disease

Abstract

Background: Statin intolerance especially myalgias can be a serious problem. Whilst it is well known that drugs that compete for Cytochrome 450 system can result in myalgias there is sparse data on the role of glucuronidation of statins contributing to statin intolerance. We report on a 60 year old male with Hypercholesterolemia (HC) who was referred for management of his HC since he had statin intolerance manifesting as myalgias and was shown to have Gilbert's Syndrome.

Case Report: Investigation of this patient revealed he had Familial Combined Hyperlipidemia with a LDL-cholesterol of 189 mg/dl. He

was also diagnosed with Gilbert's Syndrome since he had elevated unconjugated bilirubin with no evidence of liver disease or hemolysis. The combination of Niacin, Cholestyramine and ezetimibe resulted in a successful decrease in his LDL-cholesterol to 114 mg/dl.

Discussion: We believe that his Gilbert's Syndrome resulted in an impairment in glucuronidation of statin drugs resulting in an increase in free drug levels and myalgias. We caution that clinicians should consider this possibility when confronted with a patient with both isolated elevations of unconjugated bilirubin and increase LDL-cholesterol levels before commencing statin therapy.

received 23.05.2015
revised 22.06.2015
accepted 27.06.2016

Bibliography

DOI <http://dx.doi.org/10.1055/s-0042-113873>
Published online: 2016
Exp Clin Endocrinol Diabetes Rep 2016; 4: e8–e10
© J. A. Barth Verlag in Georg Thieme Verlag KG
Stuttgart · New York
ISSN 2196-7407

Correspondence

I. Jialal, MD, PHD, FRCPath, DABCL

Director, Laboratory for Atherosclerosis and Metabolic Research
UC Davis Medical Center
95817, Sacramento, CA
ijialal@ucdavis.edu

Introduction

The introduction of statin therapy in clinical medicine has resulted in a significant reduction in cardiovascular (CVD) morbidity and mortality. The safety of statin therapy in patients with Gilbert's Syndrome (GS) has not been carefully documented in any series of patients. In this report, we describe a patient with GS who was statin intolerant and suggest that in such patients who cannot glucuronidate statin drugs adequately, the possibility of muscle symptoms and signs may be increased due to increase in active drug levels. Since data suggest an inverse relationship between unconjugated bilirubin levels and CVD we briefly review this topic.

Case Report

A 60 year old male was referred to the Metabolic Clinic at the VA Medical Center in 2008 with hyperlipidemia and statin intolerance manifest as myalgias and weakness. He had been tried on pravastatin, simvastatin and atorvastatin and

could not tolerate any of these medications because of these symptoms. The referring physician did not assay statin levels in this patient. He had a positive family history of premature heart disease but none of his family members were available for evaluation. Physical examination and laboratory tests revealed a normal blood pressure (125/75 mmHg), a body mass index of 29.5 kg/m², no tendon xanthoma, a small multinodular goiter. Also all peripheral pulses were palpable with no bruits and cardiac examination was normal with no evidence of aortic stenosis. Relevant laboratory values since 2008 are shown in **Table 1**. There is evidence of hyperlipidemia with a total cholesterol (TC) of 258 mg/dl, LDL-cholesterol (LDL-C) of 189 mg/dl and an apolipoprotein B level of 147 mg/dl. There were no obvious secondary cause of hyperlipidemia as evidenced by the clinical examination, a normal TSH level of 2.4 mIU/ml (normal: 0.4–5.0), no albuminuria, and normal serum albumin and alkaline phosphatase levels. He had no evidence of liver dysfunction on repeated testing and normal hemoglobin, reticulocyte count, haptoglobin and lactate dehydrogenase levels. Screening for

License terms

Table 1 Salient Laboratory Results (Reference ranges in parentheses).

TEST	PATIENTS	RESULTS
Total Bilirubin (0.3–1.2 mg/dl)	2.3	2.0
Direct(conjugated) Bilirubin (0.1–0.4 mg/dl)	0.2	0.2
Indirect(Unconjugated) Bilirubin (0.2–0.8 mg/dl)	2.1	1.8
Serum Albumin (3.3–4.8 g/dl)	4.5	4.3
Alanine Aminotransferase (5–55 IU/L)	22	27
Aspartate Aminotransferase (8–42 IU/L)	24	25
Alkaline Phosphatase (37–107 IU/L)	70	77
Hemoglobin (14–18 g/dl)	13.7	16.0
Reticulocytes (0.7–2.9%)	0.48	1.1
Haptoglobin (34–200 mg/dl)	181	162
Lactate Dehydrogenase (90–202 IU/L)	125	143
Creatinine (0.5–1.1 mg/dl)	1.1	1.1
Urea Nitrogen (8–26 mg/dl)	11	13
Plasma glucose (74–118 mg/dl)	108	93
Total Cholesterol (<200 mg/dl)	258	191
Plasma Triglycerides (<150 mg/dl)	85	82
Low-density lipoprotein Cholesterol (<130 mg/dl)	189	114
HDL-cholesterol (>40 mg/dl)	52	60

Results shown at referral in 2008 and in 2015 respectively

viral hepatitis A, Band C were negative and both platelet and leucocyte counts were normal. All these tests did not change between 2008 and May, 2015. A diagnosis of GS was made based on the increased total and indirect bilirubin levels with no evidence of liver disease or hemolysis over this 7 year period. In 2008 he was started on cholestyramine, niacin, ezetimibe and low dose aspirin and he is currently taking cholestyramine 8 g/d, niacin 2 g/d, ezetimibe 5 mg/d and aspirin 81 mg on alternate days. His most favorable lipid profile reveals a TC of 191 mg/dl, LDL-C of 114 mg/dl and an apolipoprotein B level of 110 mg/dl. Over this 7-year period he has not experienced a cardiovascular event.

Discussion

This patient has both hypercholesterolemia and GS. The diagnosis of GS was made on the basis of an increase in both unconjugated and total bilirubin over this 7 year span without any evidence of liver disease or hemolysis as evidenced by his laboratory tests over this 7-year period [1–3]. GS, first described by Gilbert and Lereboullet in 1901, is characterized by mild unconjugated hyperbilirubinemia (usually <4.9 mg/dl) without evidence of hemolysis and liver disease [1–3].

Unconjugated bilirubin is the main product of heme metabolism and is conjugated in the liver mainly by the isoenzyme of uridine diphosphate (UDP)glucuronosyl transferase (UGT1A1) to conjugated bilirubin which can be secreted in bile [2]. GS is an autosomal recessive disorder that appears to effect between 5–10% of Caucasian people. The predominant causative mutation is a dinucleotide sequence insertion in the TATA box of the UGT1A1 promoter [1–3]. The insertion of TA to the sequence A(TA)₆TAA to A(TA)₇TAA results in a reduction in enzyme activity to 10–30% of normal.

GS is usually an asymptomatic disorder. However the use of certain drugs such as irinotecan, a drug used in cancer chemotherapy which acts by preventing DNA from unwinding by inhibition of topoisomerase, or certain protease inhibitors, can result in clinical toxicity in patients with GS [1–3]. The active metabolite of irinotecan, SN-38, is glucuronidated which may result in seri-

ous adverse reactions, including myelosuppression with neutropenia and severe diarrhea in patients with GS since its clearance is impaired.

In a case report in 1994, of a patient with familial hypercholesterolemia with possible GS, there was no adverse reaction with statin therapy (pravastatin and simvastatin) [7]. However the work-up to rule out hemolysis was not complete since hemoglobin, haptoglobin and LDH levels were not reported and the concentration of bilirubin (5.4 mg/dl) was in excess of the range reported in most series of GS [1–3, 8, 9]. In the patient with statin intolerance reported here, there may have been impaired clearance of statins by glucuronidation given the deficiency in UGT1A1 found in GS preventing lactonization. This may result in higher levels of the open active form of the statin leading to myalgias and weakness [4–6]. In the presence of both hypercholesterolemia and GS, it would be prudent to carefully monitor for toxicity when prescribing statin drugs. Whilst most are familiar with the interaction of statins with drugs that inhibit or compete with cytochrome 450 (cyclosporine, erythromycin, ketoconazole etc) [5], we want to draw attention to another potential cause of statin-induced myalgias. Another pertinent issue with respect to clinical lipidology is the interaction of the fibrate, gemfibrozil with most statins by impairing glucuronidation of statins and this problem could be further accentuated in Gilbert's Syndrome due to the enzymopathy. Fortunately, fenofibrate in combination with statins do not impair statin clearance and hence is the safer choice if fibrate therapy is considered [5, 6].

In a series of patients with GS (n=22 and n=59 matched controls), the investigators documented increased antioxidant defense and decreased biomarkers of inflammation, as well as significantly lower total and LDL-cholesterol levels in GS patients compared with controls [8, 9]. No plausible mechanism was provided for the decrease in LDL-cholesterol levels. Since most patients with GS will not have elevated LDL-cholesterol this problem will only surface if the patient has undesirable LDL-cholesterol requiring statin therapy. However, in patients with GS like our patient, who cannot tolerate statin therapy, other therapies including the recently ushered in PCSK9 Inhibitor therapy offer reasonable alternatives to achieve LDL-cholesterol goals.

The association of increased unconjugated bilirubin levels and lower risk of CVD is of interest. This topic was recently reviewed in depth [10]. There appears to be a significant reduction in CVD risk in patients with GS. This has been ascribed to the antioxidant action of unconjugated bilirubin, lower levels of LDL-cholesterol, potential anti-inflammatory effects of bilirubin, and improvement of endothelial function [10–12]. However a recent Mendelian randomization study coupled to a meta-analysis failed to confirm the decreased risk for CVD for patients with genetically elevated unconjugated bilirubin [13].

Much further work is required to confirm the hypothesis that unconjugated bilirubin is cardio-protective. Until then, patients with GS should have cholesterol-lowering therapy consistent with current guidelines but be aware that in certain patients with GS the issue of statin intolerance needs to be considered.

Novelty Statement

This is the first report of statin intolerance (myalgias) in a patient with both Gilbert's Syndrome (UDPGT deficiency) and hypercholesterolemia due to impaired glucuronidation of statins.

Conflict of interest: None.

References

- 1 Sticova E, Jirsa M. New Insights in Bilirubin metabolism and their clinical implications. *World J Gastroenterol* 2013; 19: 6398–6407
- 2 Erlinger S, Arias IM, Dhumeaux D. Inherited disorders of Bilirubin transport and conjugation: new insights into molecular mechanisms and consequences. *Gastroenterology* 2014; 146: 1625–1638
- 3 Strassburg CP. Hyerbilirubinemia Syndromes (Gilbert-Meulengracht, Crigler-Naggar, Dubin –Johnson and Rotor syndromes. Best practice and research clinical. *Gastroenterology* 2010; 24: 555–571
- 4 Preuksaritanont T, Subrmanian R, Fang X et al. Glucurodination of statins in animals and humans: A novel mechanism for statin. *Lactonization Drug Metabolism and Disposition* 2002; 30: 505–512
- 5 McKenney JM, Ganz P, Wiggins B et al. Statins Chapter 22:253–280 in *Clinical Lipidology, A companion to Braunwald's Heart Diseases* by CM Ballantyne. Saunders Press; 2009
- 6 Vaughan CJ, Gottto AM. Update on Statins. *Circulation* 2004; 110: 886–892
- 7 Cummings MH, Watts GF. Drug Treatment of Hypercholesterolemia in a patient with Gilbert's syndrome. *Ann Clin Biochem* 1994; 31: 383–385
- 8 Boon AC, Hawkins CL, Bisht K et al. Reduced circulating oxidized LDL is associated with hypocholesterolemia and enhanced thiol status in Gilberts syndrome. *Fee Radic Biol and Med* 2012; 52: 2120–2127
- 9 Wallner M, Marculescu R, Doberer D et al. Protection from age-related increase in lipid biomarkers and inflammation contributes to cardiovascular protection in Gilberts syndrome. *Clin Sci* 2013; 125: 257–264
- 10 Kundur AR, Singh L, Bulmer AC. Bilirubin, platelet activation and heart disease: A missing link to cardiovascular protection in Gilbert's Syndrome. *Atherosclerosis* 2015; 239: 73–84
- 11 Lin JP, O'Donnell CJ, Schwaiger JP et al. Association between the UGT1A1*28 allele, bilirubin levels and coronary artery disease in the Framingham Heart Study. *Circulation* 2006; 114: 1476–1481
- 12 Vitek L, Jirsa M, Brodanova M et al. Gilberts Syndrome and ischemic heart disease: a protective effect of elevated bilirubin. *Atherosclerosis* 2002; 160: 449–456
- 13 Stender S, Frikke-Schmidt R, Nordestgaard BG et al. Genetically elevated Bilirubin and risk of ischemic heart disease: Mendelian Randomization studies and a meta-analysis. *J Intern Med* 2013; 273: 59–68