 DOI: 10.5578/khj.26296

An Unexpected Cause of Hepatotoxicity and Myopathy in A Patient With Coronary Artery Disease: It Is Not Statin

Gamze Babur Güler1, Ekrem Güler1, Gültekin Günhan Demir1, Hacı Murat Güneş1, Zeynep Işıl Uğurad2, Öykü Önal Musallar3

1 İstanbul Medipol Üniversitesi Tıp Fakültesi, Kardiyoloji Anabilim Dalı, İstanbul, Türkiye
2 Istinye Devlet Hastanesi, Psikiyatri Kliniği, İstanbul, Türkiye
3 Istanbul Medipol Üniversitesi Tıp Faültesi, Psikiyatri Anabilim Dalı, İstanbul, Türkiye

ABSTRACT

Sertraline is a selective serotonin reuptake inhibitor proven to be safe and effective for the treatment of depression in patients with coronary artery disease. Although nausea, diarrhea and dyspepsia are common adverse effects, less frequent reactions such as maculopathy, hepatotoxicity, rhabdomyolysis have also been reported. In patients receiving multi-drugs for co-morbid conditions (heart failure, coronary artery disease etc.) these side effects can be underdiagnosed. In this report, we present a patient with coronary artery disease and elevated liver function tests and skeletal muscle enzymes who had multiple admissions and prolonged follow-up in the emergency room due to elevated creatine kinase and creatine kinase-MB levels which delayed his appropriate management including discontinuation of sertraline instead of statin.

Keywords: Coronary artery disease, hepatotoxicity, myopathy, sertraline.

Koroner Arter Hastalığı Olan Bir Hastada Beklenmedik Bir Hepatotoksisite ve Miyopati Nedeni: Statin Değil

Gamze Babur Güler1, Ekrem Güler1, Gültekin Günhan Demir1, Hacı Murat Güneş1, Zeynep Işıl Uğurad2, Öykü Önal Musallar3

1 İstanbul Medipol Üniversitesi Tıp Fakültesi, Kardiyoloji Anabilim Dalı, İstanbul, Türkiye
2 Istinye Devlet Hastanesi, Psikiyatri Kliniği, İstanbul, Türkiye
3 Istanbul Medipol Üniversitesi Tıp Faültesi, Psikiyatri Anabilim Dalı, İstanbul, Türkiye

ÖZET

Sertralin koroner arter hastalığına eşlik eden depresyon durumlarında etkinliğini ve güvenirliliğini kanıtlamış bir selektif serotonin gerialım inhibitördür. Sık görülen yan etkileri yanında (bulantı, ishal, dispepsi) daha nadir görülen (makulopati, hepatotoksisite, rabdomiyoliz) gibi yan etkileri de bildirilmiştir. Çoklu ilaç kullanımının sık olduğu hastalarda (kalp yetersizliği, koroner arter hastalığı gibi) depresyon tedavisinde sertralin kullanımına bağlı yan etkiler gözden kaçabilmektedir. Biz karaciğer fonksiyon testleri ve kas enzimleri yükselmiş bir koroner arter hastasında sertralinin; statinlerden sonra etyolojık ajan olarak değerlendirildiği ve bu surede kreatin kinaz, kreatin kinaz-MB yüksekliği nedeniyle uzamış acil servis takipleri olan bir vakayı sunuyoruz

Anahtar Kelimeler: Koroner arter hastalığı, hepatotoksisite, miyopati, sertralin.

Geliş Tarihi: 02.04.2016 - **Kabul Tarihi:** 12.04.2016

Yrd. Doç. Dr. Gamze Babur Güler

İstanbul Medipol Üniversitesi Tıp Fakültesi,
Kardiyoloji Anabilim Dalı,
İstanbul, Türkiye
E-mail: gamzebabur@hotmail.com

Case Report:

A 46-year-old male patient with complaints of chest pain and fatigue was admitted to our outpatient clinic. His medical history was unremarkable except primary stenting in the right coronary artery for inferior myocardial infarction in January 2014. He was on clopidogrel 75 mg, metoprolol 50 mg, ramipril 5 mg, acetylsalicylic acid 100 mg and atorvastatin 20 mg therapy. The patient had suffered symptoms related with anxiety disorder (fear of death, sense of refractory chest pain, multiple hospital admissions) after acute coronary syndrome (ACS) so control angiography had been performed which revealed patency of the stent. Consultant psychiatrist had prescribed sertraline 50 mg once a day which was later increased 100 mg once a day. Despite most of his symptoms related to anxiety disorder had improved significantly with sertraline, his admissions to emergency room for chest pain persisted. Detection of elevated creatine kinase (CK) and creatine kinase-MB (CK-MB) levels at his multiple visits led to prolonged and repeated cardiac troponin follow-ups which were all negative. Prolonged ER follow-ups for serial testing gave rise to increased anxiety. Meanwhile his fatigue persisted. On admission to our clinic, his laboratory findings were as follows; CK (733,2 U/L (24-170)), Lactate dehydrogenase (LDH) (546 U/L (225-450)), Aspartate *aminotransferase* **(**AST) (93,6 U/L (0-35)), Alanine transaminase (ALT) (168,1 U/L (0-45)), *Gamma-glutamyl*transpeptidase (GGT) (63,6 U/L (0-55)). His medical history did not include any abnormalities (history of hepatitis, active infection, vigorous exercise) having potential association with those high levels. Thereafter his statin dose was decreased by half-dose. Six weeks later, follow-up visit revealed insignificant decreases in laboratory tests as follows: [CK (720 U/L(0-200)), CKMB (32 U/L (0-25)), AST (50 U/L (0-40)), ALT (77 U/L (0-50)), LDH (356 U/L (0-225)), GGT (51 U/L (0-61))] so liver ultrasound exam, serological markers for hepatitis, prothrombin time and bilirubin tests were evaluated and no abnormality was detected. Then the patient was consulted with psychiatry and sertraline was replaced with a selective serotonin reuptake inhibitor (SSRI) excreted via kidney. His liver tests performed 8 weeks later were within normal ranges [AST (40 U/L (0-40)), ALT (0-31 U/L (7-49)), GGT (26 U/L (10-71) as well as his CK (174 U/L (20-190)) and CK-MB (0-30 U/L (0-25))] levels. Statin therapy was re-initiated and his liver function tests were not elevated.

Discussion:

SSRIs are widely prescribed agents for depression treatment due to less common cardiovascular side effects (tachycardia, ortostatic hypotension) than old-generation tricyclic antidepressants[1]. Sertraline, a popular member of this group, was shown to be safe and effective for depression in patients with heart disease[2]. SADHART (Sertraline Antidepressant Heart Attack Randomized Trial) trial compared sertraline and placebo in patients diagnosed with depression within 30 days after acute coronary syndrome and demonstrated that sertraline was a safe and well-tolerated agent[3]. Although growing numbers of evidence confirmed safety of sertraline, the number and variety of reported adverse effects are increasing. In this report, we aimed to show that sertraline therapy induced hepatotoxicity and myositis in a patient with coronary artery disease whose appropriate diagnosis and treatment were delayed due to concurrent statin therapy.

Multi-drug use is common in patients with heart diseases due to comorbidities so concerns for drug interaction and safety ensue in this patient population. In an invitro study, it was showed that sertraline is metabolized by multiple enzymes as cytochrome isoforms[4]. Sertraline has mild effects on inhibiton of CYP isoenzymes thus it is associated with uncommon drug-drug interactions[5]. To our knowledge, there is no data about additive effect of sertraline and statin use with regard to liver and muscle toxicity. However, it is likely to occur when dominant hepatic metabolism for both of these drugs are taken into account. In our patient, although statin therapy was interrupted, transaminase levels remained elevated but mildly decreased.

The most commonly observed adverse events associated with the use of sertraline were nausea, diarrhea/loose stools and dyspepsia; male sexual dysfunction (mainly delayed ejaculation); insomnia and somnolence; tremor; increased sweating and dry mouth; and dizziness in product information[6]. Incidence of asymptomatic increases in serum transaminases with sertraline use is 0.5 %, meanwhile acute fatal hepatitis related to sertraline use had been reported in the literature[7]. Hepatotoxic effects of sertraline comprise complex mechanisms but the most attributed ones include apoptosis induced by prolonged endoplasmic reticulum stress[8] and apoptosis mediated by mitogen-activated protein kinase signaling pathways[9]. It is not surprising to see hepatotoxic effects of a drug which is highly metabolized by liver but the underlying mechanism for skeletal muscle injury remains to be enlightened. Rhabdomyolysis in a 71-year-old patient

with dementia was claimed to be induced by vasoconstriction/vasospasm associated with sertraline and comorbidities as the underlying cause of muscle ischemia[10].

Conclusion:

Mechanisms for liver and muscle toxicity associated with sertraline use remain to be unclear. When co-existence of coronary artery disease and psychiatric disorders are taken into consideration, it would be wise to emphasize that statin-sertraline combination seems to be an issue both cardiologists and psychiatrists need to be cautious about. We suggest to keep in mind the risk of hepatotoxicity and myositis associated with sertraline use in this specific but common patient population.

Conflict of Interest: The authors report no conflict of interest. The authors alone are responsible for the content and writing of paper.

References

1-Parissis J, Fountoulaki K, Paraskevaidis I, Kremastinos DT. Sertraline for the treatment of depression in coronary artery disease and heart failure. Expert Opin Pharmacother (2007) 8 (10):1529-1537.

2-Shelıne YI, Freedland Ke, Carney Rm. How safe are serotonin reuptake inhibitors for depression in patients with coronary heart disease? Am J Med (1997) 102(1):54-59.

3-Shapiro PA, Lespérance F, Frasure-Smith N, O'Connor CM, Baker B, Jiang JW, et al. An open-label preliminary trial of sertraline for treatment of major depression after acute myocardial infarction (the SADHART trial): Sertraline Anti-Depressant Heart Attack Trial. Am. Heart J (1999) 137 (6):1100-1106.

4-Obach RS, Cox LM, Tremaine LM. Sertraline is metabolized by multiple cytochrome P450 enzymes, monoamine oxidases, and glucuronyl transferases in human: an in vitro study. *Drug Metab. Dispos.* 2005 **33** (2): 262–70.

5-Lane Rm. Pharmacokinetic drug interaction potential of selective serotonin reuptake inhibitors. Int. Clin. Psychopharmacol (1996) 11(Suppl. 5):31-61.

6-Product Information. Zoloft (sertraline hydrochloride) US physician prescribing

information. New York: Pfizer, 2012

7-Fartoux-Heymann L, Hézode C, Zafrani ES, Dhumeaux D, Mallat. A Acute fatal hepatitis related to sertraline. J Hepatol (2001) 35 (5):683-684.

8-Chen S, Xuan J, Couch L, Iyer A, Wu Y, Li QZ, Guo L. Sertraline induces endoplasmic reticulum stress in hepatic cells. Toxicology (2014) 322:78-88.

9-Chen S, Xuan J, Wan L, Lin H, Couch L, Mei N, et al. Sertraline, an antidepressant, induces apo-ptosis in hepatic cells through the mitogen-activated protein kinase pathway. Toxicol. Sci (2014) 137 (2); 404–415.

10-Gareri P, Segura-García C, De Fazio P, De Fazio S, De Sarro G. Sertraline-Induced Rhabdomyolysis in an Elderly Patient with Dementia and Comorbidities. Ann Pharmacother (2009) 43(7):1354-1359.