

## Warfarin과 Simvastatin/Gemfibrozil의 약물 상호 작용 : 높은 수치의 ALT/AST, 횡문근 용해와 급성 신장 장애

윤현옥 · Babatunde Osun\*  
미국 하워드 대학교 약학대학

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## Drug Interaction of Warfarin with Simvastatin / Gemfibrozil : high levels of ALT/AST, rhabdomyolysis and acute renal failure

Hyonok Yoon and Babatunde Osun\*

College of pharmacy, Howard University  
2300 Fourth Street, N.W., Washington D.C. 20059, U.S.A

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이 증례는 드물게 보는 경우로 simvastatin과 gemfibrozil을 오랫동안 함께 복용했음에도, 특이한 문제가 발견되지 않았지만, 이들을 warfarin와 함께 치료하는 경우, 아주 높은 alanine aminotransferase (ALT), aspartate aminotransferase (AST) 혈중 농도, rhabdomyolysis, 급성 신장 장애가 발생하였다. 그 후, Simvastatin와 gemfibrozil을 복용 중단시켰더니, ALT/AST는 빠르게 정상수치로 돌아온 경우이다. 이 증례 보고서는 의료인들에게 simvastatin과 gemfibrozil을 함께 혹은 따로 warfarin과 함께 복용시켜 치료할 경우, creatine phosphokinase (CPK) 와 creatinine 혈중 수치들을 포함하여 ALT/AST 농도들을 주의 깊게 모니터하도록 경각심을 주고자 한다. .

□ Key words - ALT, AST, rhabdomyolysis, acute renal failure, simvastatin, gemfibrozil, warfarin

Simvastatin is a selective, competitive 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase, the rate limiting enzyme that converts 3-hydroxy-3 methylglutaryl-coenzyme A to mevalonate, a precursor of sterols in cholesterol biosynthesis.<sup>1)</sup> It has been used to treat hyperlipidemias to decrease levels of total cholesterol, low-density-lipoprotein(LDL)-cholesterol, triglycerides(TC), apolipoprotein B and to elevate high-density-lipoprotein(HDL)-cholesterol level.<sup>2, 3)</sup>

In monotherapy of simvastatin, rhabdomyolysis with acute renal failure has occurred rarely,<sup>4)</sup> but risk of it is increased with concurrent use of gemfibrozil, fibric acid derivatives, niacin, danazol or strong Cytochrome P450

(CYP)3A4 inhibitors like amiodarone, clarithromycin, cyclosporine, erythromycin, telithromycin, itraconazole, ketoconazole, nefazodone, grapefruit juice in large quantities, verapamil, indinavir, nelfinavir, ritonavir and posaconazole.<sup>5 6 7 8 9-15 16)</sup>

Gemfibrozil is a fibric acid to treat hypertriglyceridemia in types IV and V hyperlipidemia for patients with greater risk of pancreatitis and not having responded to exercise and dietary intervention because it can inhibit lipolysis and reduce subsequent hepatic fatty acid and uptake as well as inhibit hepatic secretion of very low density lipoprotein(VLDL).<sup>17, 18)</sup>

However, the disadvantage of gemfibrozil is that there is a possibility of raising serum transaminase levels and being associated with rare myositis or rhabdomyolysis.<sup>19)</sup>

This report presents a case of rhabdomyolysis that is complicated with acute renal failure and significantly high levels of AST/ALT being associated with the con-

Correspondence to : Babatunde Osun  
College of Pharmacy, Howard University 2300  
4<sup>th</sup> Street, NW, Washington, DC 20059, U.S.A.  
Tel: 1-202-806-9076, Fax: 1-202-806-4636  
E-mail: Babatunde.Osun@va.gov

comitant use of simvastatin, gemfibrozil and warfarin.

## CASE REPORT

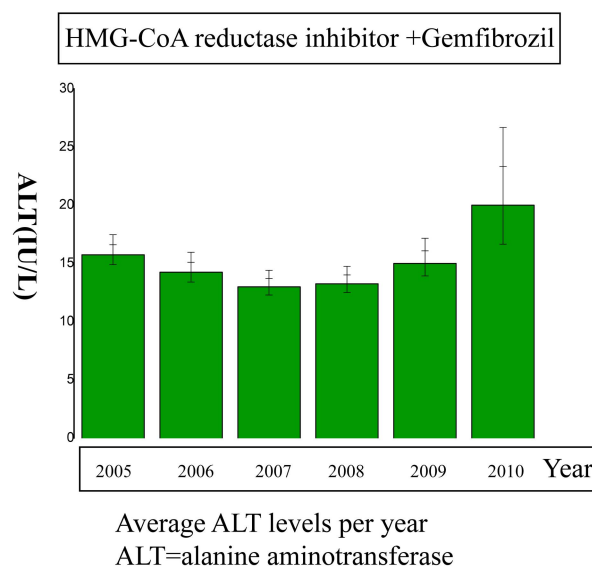
An 81-year-old-Asian male who was 179cm height, 75.7 kg weight with permanent pacemaker, chronic kidney disease {Serum creatinine (Scr) 1.73 in 2010}, anemia, hypertension, embolism of artery, prostate cancer, hyperlipidemia, arterial fibrillation and chronic pain was admitted to the emergency department (ED) of a hospital. His complaint was of blue toe syndrome, dizziness, bilateral leg pain and weakness 15 days after starting warfarin when international normalized ratio (INR) was 1.1 and Scr was 1.66. He was advised to go to the ED immediately by his primary doctor who had checked his hematologic data.

He was taking several medications prior to admission such as aspirin 81 mg tablet orally once daily, nortriptyline 10 mg capsule orally once daily but occasionally at bedtime, acetaminophen-codeine 300-30 mg orally every 4 hours as needed for pain, while not exceeding 6 tablets in 24 hours, warfarin 2.5 mg orally as directed by anticoagulation service, simvastatin 80mg orally every evening, lisinopril 10mg orally once daily, gemfibrozil 600 mg orally twice daily.

The patient had been relying on lovastatin since 2004, gemfibrozil since 2005. And the simvastatin was switched from lovastatin since 2007. He had no adverse effects such as rhabdomyolysis with these medications until administration of warfarin. His previous ALT history was between 14 and 18 in 2005, 12-16 in 2006, 11-14 in 2007 and 2008, 12-17 in 2009, 13-29 in 2010 on routine outpatient primary medical doctor check (Figure 1).

Review of systems was negative with headache, fever, chills, dyspnea and chest pain. He had a history of 6 years of smoking before the age of 70 years, 1 glass of wine drinking at night regularly and no history of illegal drugs use.

On admission, his vital signs were stable such as blood pressure 135/75, pulse 77, temperature 36.9C, respiratory rate 18, SpO2 97% and his chest was clear. He was afebrile, had mild leg muscle tenderness, and labs were Scr



**Fig. 1. Average ALT levels in each year from 2005 to 2010 when the patient had taken HMG-Co A reductase inhibitor and gemfibrozil together.**

3.41, AST 1277, ALT 626, normal T bill, CPK 453, white blood count (WBC) 3, red blood count(RBC) 6. In addition, his lab data were Scr 1.96, AST 1045, ALT 490, normal T bill, CPK 356 at outpatient setting one day before his admission of hospital. He was anuric.

In ED, simvastatin and gemfibrozil were kept away but warfarin was continued. The patient was injected with IV fluids and was placed with Foley's catheter for acute urinary retention. After getting placement of 3 ways of catheter, the patient had few clots and frank blood. He was irrigated strongly to remove old clots.

It was the assessment of suspected concurrent use of simvastatin and gemfibrozil together with warfarin to induce rhabdomyolysis, transaminitis and acute renal failure.

After simvastatin and gemfibrozil were discontinued, his AST, ALT and CPK levels had been reduced significantly and gradually (Figure 2, 3, 4) when intravenous fluids of 2 L of normal saline were injected within first 4 hours followed by 100 mL/hour of fluid injection. The abnormal levels of his laboratory results and several symptoms were gradually improved within 3 days except the Scr (Figure 5). His level of Scr continued to

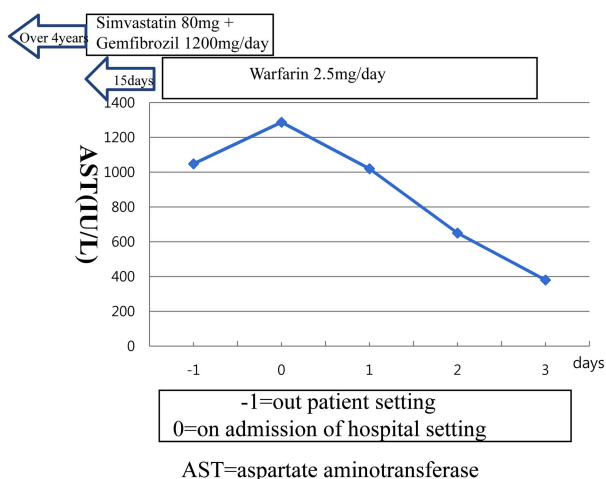


Fig. 2. Changes in AST levels from 1 day before the admission to the 3rd day of hospital admission (Arrows indicate that Simvastatin/Gemfibrozil together were taken over 4years until the admission and warfarin was started 15days before the admission day).

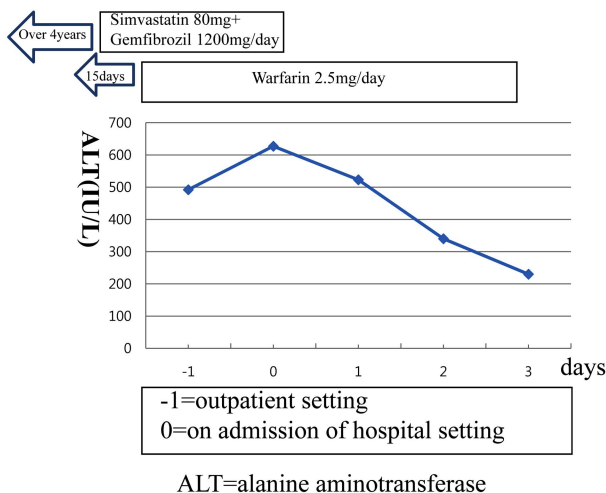


Fig. 3. Changes in ALT levels from 1 day before the admission to the 3rd day of hospital admission (Arrows indicate that Simvastatin/Gemfibrozil together were taken over 4years until the admission and warfarin was started 15days before the admission day).

increase and he was led to anuric. Triple lumen quinton was placed in his right femoral vein. He began to receive hemodialysis from the next day of admission. His renal failure was improved after the peak of serum creatinine on the 2nd day since admission (Figure 5). Urine formation was also increased gradually from anuria.

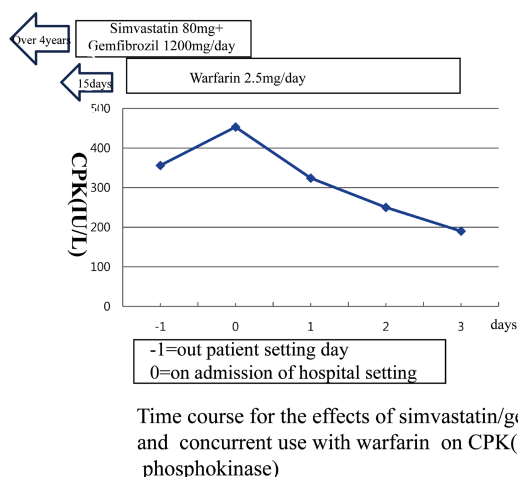


Fig. 4. Changes in CPK levels from 1 day before the admission to the 3rd day of hospital admission (Arrows indicate that Simvastatin/Gemfibrozil together were taken over 4years until the admission and warfarin was started 15days before the admission day).

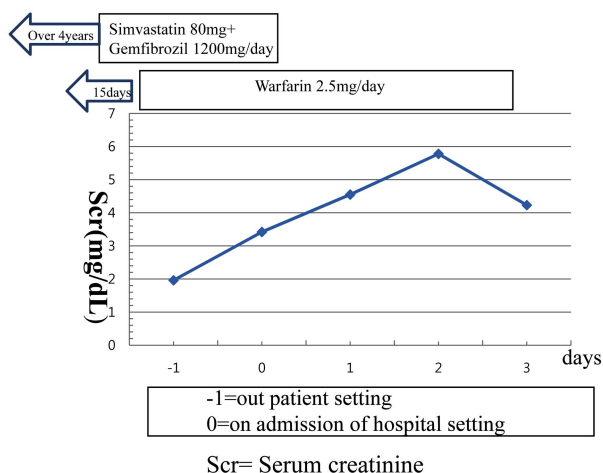


Fig. 5. Changes in Scr levels from 1 day before the admission to the 3rd day of hospital admission (Arrow indicates that Simvastatin/Gemfibrozil together were taken over 4years until the admission and warfarin was started 15days before the admission day).

His blue toe syndrome due to cholesterol microembolization had been rarely (< 0.1%) described with warfarin type anticoagulants although this syndrome was considered to be caused by either hemorrhage into atheromatous plaques or by the weakening of the fibrin meshwork. This syndrome had also been improved considerably after several days of admission.

The patient's prothrombin INR which was elevated

up to 3.2 on admission day returned to the desired therapeutic range on the 2nd day once simvastatin and gemfibrozil were discontinued.

## DISCUSSION

This is a report of abnormal liver function inducing high levels of AST/ALT and rhabdomyolysis including renal failure due to the interactions of simvastatin, gemfibrozil and warfarin.

This case implies several possible causes that induce increase in transaminases, Scr and CPK, such as history of smoking and drinking, age, prostate cancer, higher dose of simvastatin, and concurrent administration of simvastatin and gemfibrozil with warfarin.

In 2010, the research to evaluate the efficacy and safety of high-dose simvastatin (80 mg daily) was conducted through comparison with low-dose (20 mg daily) cases. High-dose simvastatin lowered LDL cholesterol level by average of 13.5 mg/dL (0.35 mmol/L) than the case of low dose. The reported cases of myopathy, including rhabdomyolysis, were significantly increased in the high-dose group (0.9% versus 0.03%; CI 6.5-109). The research showed that 7 confirmed cases were rhabdomyolysis (defined as CPK > 40 times the upper limit of normal (ULN) with the evidence of end-organ damage (eg, doubling of plasma creatinine)) and another 7 cases were with CPK levels higher than 40 times ULN in the high-dose group.<sup>20)</sup> In this case, the patient had taken high-dose simvastatin (80 mg daily) for over several years, but signs of rhabdomyolysis were not found until administration of warfarin.

The Food and Drug Administration (FDA) Adverse Event Reporting System (AERS) database demonstrated that the rate of rhabdomyolysis was increased 10-fold more than when the HMG-CoA reductase inhibitors combined with gemfibrozil.<sup>21)</sup> Among the 866 cases of rhabdomyolysis in the AERS database, 384 (44%) were associated with the concomitant use of gemfibrozil. The concomitant administration of gemfibrozil (600 mg twice daily × 3 days) and simvastatin (40 mg single dose on day 3) elevated simvastatin area

under the curve (AUC) and half-life by 35% and 74%, respectively. Also, the AUC, Cmax, and half-life of simvastatin acid (active form of parent drug), are increased by approximately 3-fold, approximately 2-fold, and 51%, respectively, compared to simvastatin with placebo in 10 healthy subjects.<sup>22)</sup> Simvastatin is metabolized by CYP3A4 and undergoes hepatic uptake via organic anion transporting polypeptide 1B1 (OATP1B1).<sup>23)</sup> Simvastatin acid is metabolized by both CYP3A4 and CYP2C8.<sup>23, 24)</sup>

Gemfibrozil is also slightly metabolized by CYP3A4. In addition, gemfibrozil and its glucuronide inhibit OATP1B1 and CYP2C8,<sup>23)</sup> so that the interaction might happen due to inhibition of this transporter or enzyme, or a combination of both.

However, the hyperlipidemia of the patient had been controlled with daily admission of HMG-CoA reductase inhibitors and gemfibrozil (1200 mg) for 6 years without any significant adverse effects such as rhabdomyolysis, abnormal kidney and liver function though many reports prohibit the use of simvastatin and gemfibrozil together to protect adverse effects.

AST and ALT are sensitive indicators of liver damage or injury from different types of diseases. ALT and AST known as transaminases, which are enzymes made in the liver. Amino acids are metabolized into protein with the help of these enzymes in the liver. ALT and AST leak into the bloodstream when the liver is injured or dying.<sup>25)</sup> ALT is specifically and solely found in the liver. Although high ALT cannot predict liver damage or disease progression, higher levels of ALT than normal range of 5 IU/L to 60 IU/L in the blood denotes that there may be hepatic inflammation and/or injury. AST is found in several organs including the liver. The normal levels of AST are between 5 IU/L to 43 IU/L. Many different abnormalities such as viral hepatitis, alcoholic liver damage, fatty liver of steatohepatitis, liver inflammation, or liver tumors can cause to increase liver enzymes above normal levels.<sup>26, 27 28, 29)</sup>

Average levels of ALT per year of this case of the patient who had taken concomitant simvastatin and gemfibrozil for 6 years showed that these were within

normal range on the patient's chart (Figure 1).

The levels of AST/ALT soared significantly during 15 days after warfarin with simvastatin and gemfibrozil were administered to the patient as shown in Figure 2 and 3.

HMG-CoA Reductase Inhibitors may enhance the anticoagulant effect of warfarin, one of Vitamin K Antagonists.<sup>30)</sup> INR values increased approximately 27% in warfarin-stable patients following the initiation of simvastatin.<sup>30)</sup> Other reports with simvastatin have described little or no effect on INR.<sup>31, 32)</sup>

Gemfibrozil have also been implicated in causing bleeding problems with oral anticoagulants.<sup>33, 34)</sup> This case did not have an adverse effect of bleeding but an increased CPK (normal 55-170) which is a side-effect of rhabdomyolysis caused from simvastatin/gemfibrozil and warfarin.<sup>35)</sup> (Figure 4)

Figure 5 described that Scr increased gradually even though the patient was treated via hemodialysis and IV fluid for 2 days after the admission. These data of Figure 2, 3, 4 showed that AST, ALT and CPK returned back abruptly. The kidney function, however, may not get back well quickly as shown in Figure 5.

The patient-specific variables, such as age, previous smoking history, prostate cancer and chronic kidney failure are not believed to induce abruptly abnormal organic damage in this case. Also, the patient's regular daily consumption of only 1 oz. of wine could not cause the unusual case of high ALT/AST, CPK, and Scr.

This case study demonstrated to report abnormal skyrocketing levels of transaminases, including rhabdomyolysis to an interaction between simvastatin, gemfibrozil and warfarin as the history of his drug regimen. It has given health providers a valuable lesson of monitoring clinical and laboratory data more carefully as well as to hold or reduce the dose of simvastatin and/or gemfibrozil when patient begins to take warfarin. Also, it is worthy to be mentioned that any significant adverse effects unobserved during long concomitant use of simvastatin and gemfibrozil are very rare.

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