Rhabdomyolysis Associated with the Combined use of Cerivastatin with Gemfibrozil and a Macrolide Antibiotic

SERİVASTATİN, GEMFİBROZİL VE BİR MAKROLİD ANTİBİYOTİĞİN BİRLİKTE KULLANILMASINA BAĞLI RABDOMİYOLİZ OLGUSU

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Summary

A 45 year old woman with diffuse myalgia, markedly increased serum myoglobin and creatine kinase levels and elevated liver function tests was admitted to the hospital. Further evaluations showed that she had rhabdomyolysis due to combined use of cerivastatin, gemfibrozil and claritromycin. After withdrawal of her medications with forced diuresis she recovered in 4 weeks time. She is now on a second step diet and under strict control with daily 10 mg pravastatin only.

Myopathy associated with rhabdomyolysis and hepatotoxicity may result from the pharmacokinetic interaction between lipid lowering drugs and macrolide antibiotics due to common use of cytochrome P450 3A4 enzyme for their metabolisms.

Key Words: Rhabdomyolysis, Lipid lowering drugs, Macrolide antibiotics

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Özet

Kırkbeş yaşında kadın hasta yaygın kas ağrısı ile hastanemize başvurusunda serum miyoglobin ve kreatin kinaz seviyelerinin belirgin yüksek, karaciğer fonksiyon testlerinin bozuk saptanması üzerine yatırıldı. İleri tetkiklerle serivastatin, gemfibrozil ve klaritromisinin kombine kullanımına bağlı rabdomiyoliz olgusu olduğu gösterildi. Almakta olduğu ilaçlar kesildi, zorlu diürez sağlandı. 4 hafta sonra hasta tamamen düzeldi. Halen ikinci basamak diyetinde olup, sadece günde 10 mg pravastatin ile sıkı kontrol altındadır.

Lipid düşürücü ilaçlar ve makrolid antibiyotiklerin birlikte kullanılması ile görülebilen rabdomiyolizin eşlik ettiği miyopati ve hepatotoksisite bu ilaçların metabolizmaları için sitokrom P450 3A4 enzimini ortak olarak kullanmaları nedeniyle aralarındaki farmakokinetik etkilenmeye bağlı olabilir.

Anahtar Kelimeler: Rabdomiyoliz, Lipid düşürücü ilaçlar, Makrolid antibiyotikler

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The hydroxymethylglutaryl-coenzyme A reductase inhibitors (HMG CoAs) are one of the most significant causes of medication induced rhabdomyolysis .The development of rhabdomyolysis is increased when the HMG-CoAs are used concurrently with certain other medications, spesifically gemfibrozil and macrolide antibiotics. We report a case of myopathy with rhabdomyolysis and hepatotoxicity from the combined use of cerivastatin, gemfibrozil and clarithromycin (1-4).

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Case Report

A 45 -year - old - woman with severe myalgia and muscle weakness was admitted to our hospital in October 2000. Her symptoms had intensified so progressively and spread from legs to shoulder and back muscles that she could not move or walk.

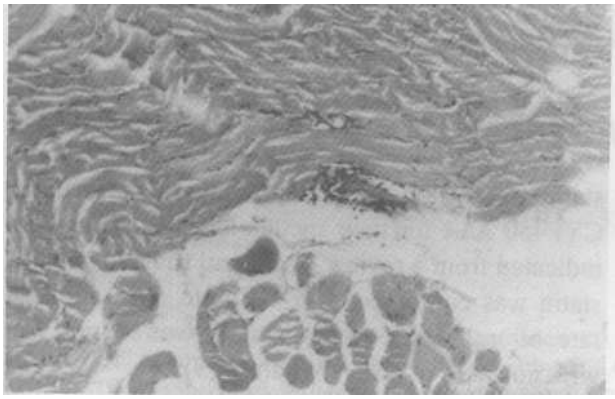

Figure 1. Mononuclear infiltration and capillary proliferation.

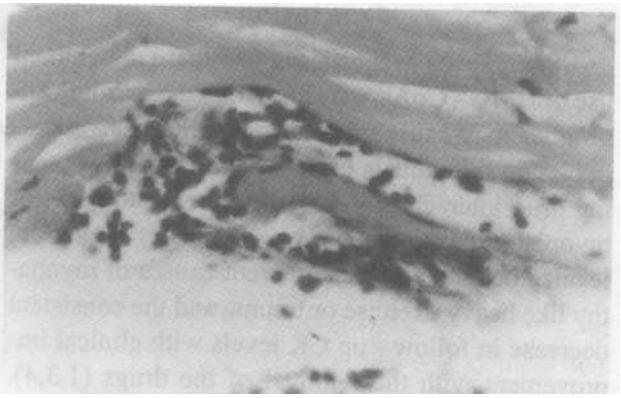

Figure 2. Mononuclear infiltration and myofibrillar degeneration with cariorexis of the nucleoli.

Nine months ago, during a routine check up, she was found to have high concentrations of serum cholesterol and triglyceride levels.She was first put on daily treatment with simvastatin at 10mg for 2 months, then Atorvastatin at 10mg for 6 months.In September 2000 she had her laboratory analysis of lipid profile. Still having high lipid and triglyceride levels, she was put on cerivastatin, 0,2mg daily and gemfibrozil, 600mg twice daily treatment. Two weeks later she also started using clarithromycin, 500mg twice daily for lower respiratory tract infection.Since then her symptoms developed.

During her admission to the hospital laboratory values were the following : Plasma cholesterol, 218mg/dl; triglyceride, 774 mg/dl; HDL-Cholesterol, 16 mg/dl; VLDL-Cholesterol, 187 mg/dl; Lp(a), 49 mg/dl (normal range 0 - 30 mg/dl); CK, 23410 U/L (normal range 0 - 190 U/L); ALT and AST, 406 U/Land 959 U/L (normal range 4 - 37 U/L) respectively; LDH, 4075 U/L (normal range 160 - 500 U/L); gamaglutamyl transferaz, 560 U/L (normal range 0 - 49 U/L); serum myoglobin, 3430 ng/ml (normal range 7 - 64 ng/ml); urine myoglobin, 2 mg/L (normal range; < 0.1 mg/L); cardiac troponin -T was negative, serum creatinine, 0.8 mg/dl (normal); serum uric acid, 3.3 mg/dl (normal range 2.3 - 8.2 mg/dl); rheumatoid factor and C - reactive protein was normal.During her stay in hospital she was consulted by a neurologist and an infectious disease specialist. Hepatic markers were negative. Antinuclear, anti DNA ,antimitochondrial and liver, kidney microsomal autoantibody titers were negative, anti-smooth-muscle autoantibody titer was 1/80 positive. In needle electromyelography motor unit potential changes with short duration, low amplitude and polyphasy of the proximal lower extremity muscles suggestted primary muscle involvement. Owing to Pierce and his colleagues the quadriceps muscle was biopsied on the third week of her admission (3). Mononuclear infiltration, myofibrillar degeneration with cariorexis of the nucleoli, vacuolization of myocytes and capillary proliferation was postulated to account for drug induced myopathy by the pathologist.(Figure 1,2).

All the medications were discontinued at once and the patient underwent forced diuresis with saline and bicarbonate.

Four weeks later her symptoms disappeared and had a normal physical examination and normal laboratory findings as follows: CK, 41 U/L; ALT, 27 U/L; AST, 26 U/L; GGT, 25 U/L; LDH, 288 U/L; myoglobin, 51 ng/ml; plasma cholesterol, 258 mg/dl; triglyceride, 899 mg/dl ;Lp(a), 40mg/dl. In Lipid electrophoresis a significant elevation of prebeta band, 66% (normal range 0 - 29.6%); decline in beta - band 20.7% (normal range; 40.7 - 71.9%); normal chylomicron and alpha bands, 0.5 and 12.4% (normal ranges 0 - 1.0 and 9.8 - 46.2 %) respectively. We concluded that she had type IV hyperlipidemia. She was put on a modified second step diet. By now she has plasma cholesterol, 177 mg/dl; triglyceride, 243mg/dl and is under strict control with a daily use of 10mg pravastatin only.

Conclusion

Spontaneous reports suggest that concomitant use of HMG - CoAs, gemfibrozil and macrolide antibiotics may cause myopathy and rhabdomyolysis in certain individuals (1,3). Support for this potential drug interaction is based on the acute onset of myopathy accompanied by extremely high CK levels, the lack of other apparent causes of myopathy like heavy exercise or trauma and the consistent decrease in follow - up CK levels with clinical improvement with the removal of the drugs (1,3,4). Pierce et al noted that significantly higher proportion of women reported to have myopathy with combination therapy as was seen in our case (3).

Cerivastatin is the last generation of the HMG - CoAs and tolerability in clinical trials did not differ from that of placebo with regard to serum CK levels (5-6). It is metabolized by a dual metabolic pathway of the cytochrome P450 (CYP450) enzyme system. CYP450 3A4 catalyzes the inactivation of simvastatin, converts atorvastatin and cerivastatin to active metabolites. Coadministration of macrolide antibiotics which inhibit this enzyme represent a potential drug interaction and should be generally avoided (6-9). Gemfibrozil is a fibric acid derivative. Fibric acid derivatives require CYP450 3A4 for their metabolism and have occasionally been associated with a syndrome that develops over days to weeks consisting of malaise, myalgias, muscle weakness and moderately to markedly elevated CK levels (2,3,9). As fibric acid derivatives and their metabolites are eliminated primarily via the renal route, these drugs are contrindicated in patients with renal insufficiency. Fibrates can sometimes be associated with elevations of serum aminotransferase levels or even frank cytolytic hepatitis (3,7,10). Hepatotoxicity by HMG - CoAs is dose -related, usually unassociated with symptoms and slowly reversible on discontinuation of the drug (7,9). Hepatotoxicity appears to be directly linked to the mechanism of the action of the drug inhibition of HMG - CoA reductase (7,9). It is theoretically possible that fibrate associated alteration of hepatic function leads to impaired elimination of cerivastatin metabolites.(7,9,10).

The relative myotoxicity of each of the fibrates, alone or combined with a statin, is unknown, as is the exact mechanism for the fibrate-statin interaction. Both classes of agents requre CYP450 3A4 for their metabolisms (9). Shepherd indicated from a review of clinical trials in which a statin was combined with a fibrate, the estimated rate of myopathic complications were only 1%, with no cases of a severe nature (9).

In conclusion we can say that rhabdomyolysis might result from the pharmacokinetic interaction between cerivastatin, gemfibrozil and macrolide antibiotic, claritromisin in our patient.

REFERENCES

1. Landesman KA, Stozek M, Freeman NJ. Rhabdomyolysis associated with the combined use of hydroxymethylglutaryl - Coenzyme A reductase inhibitors with gemfibrozil and macrolide antibiotics .Conn Med 1999; 63(8) :455-7.
2. Bizzaro N, Bagolin E, Milani L, Cereser C, Finco B.Massive rhabdomyolysis and simvastatin. Clin Chem 1992; 38 (8): 1504.
3. Pierce LR, Wysowski DK, Gross TP. Myopathy and rhabdomyolysis associated with lovastatin - gemfibrozil combination therapy.JAMA 1990; 264 (1) :71-5.
4. Rodriquez ML, Mora C, Navarro JF. Cerivastatin -induced rhabdomyolysis .Ann Intern Med 2000; 132 (7): 598.
5. Stein EA. Extending therapy options in treating lipid disorders:a clinical review of cerivastatin, a novel HMG - CoA reductase inhibitor. Drugs 1998; 56 (Suppl 1) :25-31.
6. Bischoll H, Heller A. Preclinical and clinical pharmacology of cerivastatin . Am J Cardiol 1998; 82 (Suppl 4B) :18-25.
7. Stone NJ, Blum CB, Winslow E. The lipid lowering drugs . In: Stone, Blum and Winslow eds. Management of Lipids in Clinical Practice IIIinois:Professional Communications, nc. 1998: 195-238.
8. Jacobson RH, Wang P, Glueck GJ. Myositis and rhabdomyolysis associated with concurrent use of simvastatin and nefazodone. JAMA 1997; 277 (4) :296-7.
9. Kannel W, Braunwald E. Therapeutic Interventions: Lipid regulating drugs and low density Lipoprotein apheresis . In: Gotto A, Pownall H eds.Manual of Lipid Disorders. Baltimore: Williams & Wilkins, 1999: 292-322.
10. Transcript: Metabolism and Endocrine Drug Advisory Committee Meeting. Rockville, MD: Food and Drug Administration; September 29, 1989.