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Rhabdomyolysis: a case study exploring the possible side effect of lipid lowering medication by a HIV positive patient taking a protease inhibitor

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This case study explores the incidence of rhabdomyolysis in a HIV positive patient that was taking a lipid lowering drug and a protease inhibitor concurrently while under chiropractic treatment for generalized muscular soreness. Dyslipidemia is a very common problem both in the general and HIV population, with many patients being prescribed lipid lowering drugs. While extremely rare, adverse effects of lipid lowering drugs have been documented to include myopathy such as rhabdomyolysis. It is imperative that chiropractors are aware of the possible adverse side effect of lipid lowering drug therapy in their patients complaining of musculoskeletal pain. It is even more important that chiropractors treating the HIV population are aware of the potential interactions between these medications and protease inhibitors to cause myopathy.
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key words: Drug induced myopathy, lipid lowering drugs, protease inhibitors, HIV infection, manual therapy

Cette étude de cas évalue l'incidence de la rhabdomyolyse chez un patient séropositif pour le VIH qui consommait en même temps des hypolipémiants et un inhibiteur de protéase alors qu'il était soigné par un chiropraticien pour des douleurs musculaires générales. La dyslipidémie est un problème très fréquent, tant dans la population générale que chez les personnes séropositives pour le VIH, en particulier chez les patients à qui on a prescrit des hypolipémiants. Bien qu'extrêmement rares, les effets indésirables des hypolipémiants ont été répertoriés et se manifestent par des myopathies, dont la rhabdomyolyse. Il est impératif que les chiropraticiens soient conscients des effets indésirables possibles des hypolipémiants chez leurs patients qui se plaignent de douleurs musculosquelettiques. Il est encore plus important que les chiropraticiens traitant des personnes séropositives pour le VIH connaissent les interactions potentielles entre ces médicaments et les inhibiteurs de protéase, qui provoquent la myopathie.
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mots clés : Médicaments causant la myopathie, hypolipémiant, inhibiteur de protéase, personne séropositive pour le VIH, thérapie manuelle

Introduction

Dyslipidemia is defined as a simultaneous increase in serum triglyceride, LDL and VLDL cholesterol levels and decrease in HDL cholesterol. This altered lipid profile is a common problem in the HIV population secondary both to protease inhibitor drug therapy and the HIV infection itself[1] as well as in other chronic metabolic diseases such as Type II Diabetes[2]. Statins and fibrates

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and two families of lipid lowering drugs widely prescribed to decrease cholesterol and triglyceride levels.[3] One of the most serious adverse effects of both of these groups of drugs is rhabdomyolysis; the breakdown of muscle cells resulting in renal damage.[4] In this article we present the case of an HIV positive patient undergoing chiropractic care for side effects associated with HIV drug therapy and fibromyalgia who developed severe rhabdomyolysis while taking a lipid lowering drug (200mg/day) and a protease inhibitor.

Case Presentation

A 36 year old man with a previous diagnosis of fibromyalgia (2003) and HIV (1988) has been under chiropractic management for musculoskeletal symptoms. Chiropractic treatment consisted of spinal manipulative therapy and soft tissue therapy to the area of complaint at each visit. The patient was on 200 mg of a lipid lowering drug in a capsule form daily, since June 2004 and has been taking Highly Active Antiretroviral Therapy (HAART) medication since March 2003. On December 2, 2004 the patient was admitted to hospital with a 3 day history of muscle weakness. Patient was found by a family member in his residence, unable to walk. Upon being admitted, the patient had no focal neurological deficits, bowel/bladder incontinence or recent trauma. He did not have any recent infections at that time, and was not on any type of exercise regime. He was not smoking, or consuming any recreational drugs or alcohol.

Upon physical examination, heart rate was 99 beats per minute, respiratory rate was 12 breaths per minute and blood pressure was 100/60. Patient's chest was clear on auscultation and there were no abdominal symptoms. His legs were not swollen. Cranial nerve exam was within normal limits. CT head scan showed no indication of hemorrhage. Radiographs showed no gas in the tissue, reducing the likelihood of necrotizing fasciitis. Urine output was 100cc, dark in colour and found positive for myoglobin. Ulcers were noted on the left calf and right shin. Laboratory work found high blood urea nitrogen levels, creatinine, high AST and ALT as well as low hemoglobin.

The patient was diagnosed with rhabdomyolysis secondary to HAART medication interaction, and was started on dialysis and IV hydration. Creatinine levels decreased to 240, and urine output levels increased to 1000cc per day. Liver enzymes gradually returned to normal during the duration of the hospital stay. The patient had an episode of hemoptysis on December 3, 2004. Based on HIV status, the patient was admitted into respiratory isolation, until Tuberculosis was ruled out. The diagnosis was changed to possible congestive heart failure with pulmonary edema secondary to uremia. The patient was discharged on December 22, 2004 and the physician felt that the episode of rhabdomyolysis was not likely due to HAART alone, therefore recommended the patient restart medications.

After hospital discharge, the follow up care recommendations were to monitor patient's blood work including electrolytes, blood urea nitrogen and creatinine until levels normalized. An infectious disease specialist recommended introducing the previous HAART regime, one medication at a time, monitoring for any adverse reactions. Chiropractic plan of management resumed with increased attention to monitor the patient for future occurrences of symptoms associated with rhabdomyolysis.

Discussion

It is difficult to discern the number of chiropractors treating HIV patients across Canada. According to a 2003 study examining complementary and alternative medicine use in HIV, there is a 19.2% prevalence of HIV positive patients seeking chiropractic care in the province of Ontario.[5] Thus, the majority of readers should be mindful instead of the patients in their practice that are being treated for dyslipidemia from other causes such as Type II Diabetes. It is important to keep in mind that in the aging population incidence of chronic metabolic syndromes are increasing with a large portion of these patients being prescribed statin or fibrate drugs. Muscle pain and weakness are two documented side effects of these two families of drugs.[6]

Dyslipidemia

Dyslipidemia, one of the modifiable risk factors of cardiovascular disease, is described as elevated serum triglyceride levels and reduced total cholesterol, LDL and HDL cholesterol. Untreated, this condition places a patient at increased risk of strokes and heart attacks. Dyslipidemia is identified in all HIV infection patients to some degree and caused by two main factors: the infection itself and

secondary to antiretroviral drug therapy.[1] The HIV infection causes elevations in circulating cytokines that modulate lipid metabolism and result in alterations in the normal lipid profile.[7–9] Changes in plasma cholesterol and serum triglyceride levels have also been observed with the use of HIV protease inhibitors including: saquinavir, indinavir, ritinavir, lopinavir, amprenavir and nelfinavir.[10,11] Romeu et al. found increases in serum triglyceride levels in over half of the patients on protease inhibitors after two years with the risk increasing in proportion to the duration of the therapy.[12] Recent data suggest that hyperlipidemia associated with protease use may result from increased production of VLDL cholesterol particles by the liver.[13,14] This accelerated production appears to be the result of the activation of lipogenic genes in the liver.

Pharmacological management of Dyslipidemia

Pharmacological management of high triglyceride levels in patients is one of the approaches recommended to lower the risk of hemorrhagic pancreatitis and coronary heart disease along with dietary modifications and exercise.[15,6,16] Fenofibrate was first introduced into the US in 1998, it is 99% protein bound with a half-life of about 20 hours. It is metabolised primarily by glucuronidation with the inactive conjugate (about 80%) excreted in the urine.[17] Unlike statin drugs that are metabolised in the liver by oxidation, there is no significant drug-drug interaction among the protease inhibitors and fibrates thus making them a reasonable first choice in the management of dyslipidemia in HIV patients.[18] The mechanism of action of fenofibrate is by activating a class of nuclear receptors known as peroxisome proliferator activated receptor alpha (PPAR-α). This stimulation results in increased production of lipoprotein lipase, HDL cholesterol and generally improved lipid transport. [10,19, 20] Four fibrate derivative drugs are currently available, they include: gemfibrozil, fenofibrate, bezafibrate and clofibrate.[19] Potential side effects of fibrates have been identified to include: muscle pain or weakness (myopathy), with or without elevated serum levels of creatine kinase, that may in rare instances progress to rhabdomyolysis and death. The exact mechanism by which these side effects occur is presently unknown. Fenofibrate has been proven to be successful for decreasing serum triglyceride, VLDL and LDL cholesterol levels as well as increasing HDL cholesterol.[21] In the US, prescriptions of fenofibrate increased more than three times between 1999 and 2002 to 11.041 million prescriptions.[22] Alskeikh-Ali et al. performed a retrospective analysis of risk for the gemfibrozil and fenofibrate from 1999 to 2002. The rate of any adverse effect for fenofibrate was determined to be 80.1 per million prescriptions. Rates of rhabdomyolysis specifically were significantly higher with gemfibrozil (59.6 per million) compared with fenofibrate (5.5 per million).[22] The exact cause of fibrate-induced myopathy is unknown.

Rhabdomyolysis

Rhabdomyolysis is a rare muscle disease in which striated muscle fibers disintegrate, excreting myoglobin in the urine.[23] If not recognized and treated promptly, complications such as acute renal failure, compartment syndrome in the affected muscle group, muscle necrosis, disseminated intravascular coagulation, arrhythmias and cardiac arrest may ensue.[24, 25] Major causes of rhabdomyolysis include crush injuries, burns, infections (including HIV), medications, drugs and exercise.[26] Signs and symptoms include nausea and vomiting, agitation, delirium, anuria, fever, myopathy, weakness, muscle pain, muscle bruising and tea/cola coloured urine.[27] Laboratory findings include elevated values of creatine kinase (more than 10 times the normal amount), white blood cells, aspartate aminotransferase, alanine aminiotransferase, lactate dehydrogenase, and myoglobinuria.[28, 29] The pathophysiology of rhabdomyolysis is related to the disintegration of skeletal muscle. Direct injury to muscle fibres or a disruption in energy consumption leads to an increase in intracellular calcium. The extra calcium results in the pathological interaction of actin and myosin causing fibre necrosis and muscle destruction.[28] Due to the concern of hepatic side effects and rhabdomyolyis, close follow up with liver enzyme tests and creatine kinase measurements are recommended 6 weeks after starting fibrate therapy and every 6 months thereafter (or if symptoms appear). The risk of side effects is more likely when combined with statin therapy especially HMG-CoA reductase inhibitors.[10] However, fenofibrate is not metabolised by cytochrome P450 and therefore their systemic availability is not expected to rise in the presence of protease inhibitors. Fenofibrate is partially biotransformed by glucuronidation and may interact with nelfinavir or ritonavir.[30]

Rhabdomyolysis Risk in the HIV positive patient

As mentioned previously in this summary, rhabdomyolysis can be a direct result of the HIV virus. In the advanced stages of HIV/AIDS disease, the patient may develop rhabdomyolysis-associated infections such as pneumocystis carinii, Toxoplasma gondii, Staphylococcus Aureus, Cryptococcus and Pyomyositis.[26] Other risk factors in this population include illicit drug use, Retrovir and alcohol abuse. HIV-associated rhabdomyolysis appears to be caused by an immunologically mediated injury rather than by direct viral invasion of the muscle.[4] Despite these direct links to the myopathy in the HIV population, another cause is becoming more prevalent. It has been noted by Carr et al. that a wide range of metabolic and morphologic alterations have surfaced among HIV patients receiving anti-viral treatment.[31] These changes include insulin resistance, redistribution of body fat and dyslipidemia. To combat these alterations in fat metabolism, an increasing number of HIV patients are also being prescribed statin and/or fibrate drugs.[31,32] There have been documented cases of rhabdomyolysis in HIV patients that have been associated with fenofibrate drug use. Fenofibrate induced rhabdomyolysis in two dialysis patients with hypothyroidism has been reported by Clouatre et al.[32] Barker et al. described a case of a diabetic patient who had a normal creatine kinase measurement before starting monotherapy with fenofibrate and then developed rhabdomyolysis.[33] Guidelines for the Evaluation and Management of Dyslipidemia in HIV infected adults receiving antiretroviral therapy have stressed that caution must be exercised when choosing lipid-lowering agents for patients receiving protease inhibitors, giving special attention to potentially dangerous drug interactions.[16]

The authors acknowledge that three confounding variables exist in the case of this patient. Between the HIV infection, the protease inhibitor and lipid lowering medication it is impossible to discern the exact cause of rhabdomyolysis. Considering that this patient was cleared to return to HAART medications and prescriptions for the lipid lowering agent after the hospital date, it is very likely that this case of rhabdomyolysis was entirely secondary to pre-existing renal failure and HIV infection alone. However, residual muscle pain and weakness might have been a result of all three factors combined.

Conclusion

The increased prevalence of dyslipidemia within the HIV population and the decreased risk of drug interactions with lipid lowering agents and protease inhibitors suggest an increased tendency for HIV infected individuals to resemble the history presented in our case. Thus, practitioners involved in the manual therapy of HIV patients should be aware of these rare but possible non-musculoskeletal causes of muscle pain and weakness in their patients. All practitioners should be reminded of these rare but possible non-musculoskeletal causes of muscle pain and weakness in their patients, currently taking lipid lowering agents.

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