RHABDOMYOLYSIS AFTER ADDITION OF DIGITOXIN TO CHRONIC SIMVASTATIN AND AMIODARONE THERAPY

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SUMMARY

Rhabdomyolysis is a well known side effect of statin therapy. Several drugs may increase its risk by drug-drug interactions. In particular, patients with heart disease receive more and more different compounds to cope with all the pathomechanisms involved and may therefore be of high risk for side effects. We report a case of rhabdomyolysis in a patient with heart failure on a multi-drug regimen caused by a drug interaction between chronic statin therapy (simvastatin), amiodarone and newly administrated digitoxin. The patient recovered fully after cessation of simvastatin therapy, the other drugs were given continuously. Potential mechanisms of this event are discussed. Most interesting in this case is that rhabdomyolysis occurred only after starting digitoxin after long-term therapy with the statin.

KEY WORDS

rhabdomyolysis, statin, digitoxin, amiodarone, drug interaction

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INTRODUCTION

Since a survival benefit in large randomized studies has been shown for statin therapy /1/ these agents are widely used for primary and secondary prevention of cardiac events. The major risk of their administration is rhabdomyolysis, a seldom but possibly lethal side effect of these compounds /2,3/. Rhabdomyolysis is a clinical syndrome that results from severe injury to skeletal muscle and an accumulation of toxic muscle products in the blood and urine, and is defined as an elevated creatine kinase (CK) level associated with organ damage (typically renal insufficiency).

Myopathy or rhabdomyolysis is most likely to occur when statins are administered with other drugs or chemicals that are themselves myotoxic or that inhibit statin metabolism. The incidence of muscle disorders increases when statins are given together with gemfibrozil, niacin, erythromycin, itraconazole, cyclosporine, diltiazem and several other drugs /4,5/.

PATIENT REPORT

We report a 62 year-old Caucasian male patient with heart failure due to ischemic cardiomyopathy. His ejection fraction was 25% due to diffuse coronary artery disease without myocardial infarction. As shown in Table 1 he has been treated since 2004 with classical multi-drug heart failure therapy consisting of angiotensin converting enzyme inhibition (ramipril), betablockade (carvedilol), diuretics (torasemide), aldosterone antagonism (spironolactone), vasodilatation (molsidomin) and anti-platelet therapy (acetylsalicylic acid, clopidogrel). Simvastatin was administered at a dosage of 40 mg per day since 2004 as standard prophylactic therapy. After recurrent ventricular tachycardias, amiodarone was started in 2004 at a chronic dosage of 200 mg per day, and he received a biventricular defibrillator. Under these measures he was classified as having stage II heart failure according to NYHA. Routinely measured laboratory values showed normal creatine kinase levels throughout the years 2004, 2005 and until August 2006 (Fig. 1). Creatinine levels were slightly elevated and fluctuated between 1.5 and 2.1 mg/dl. In order to complete heart failure therapy, digitoxin was added in August 2006 at a daily dosage of 0.07 mg.

TABLE 1

Patient's medication at time of admission

Drug	Dosage/day	Applied since
Torasemide	20 mg	2004
Ramipril	5 mg	2004
Amiodarone	200 mg	2004
Carvedilol	2 x 25 mg	2004
Spironolactone	25 mg	2004
Molsidomine	2 x 8 mg	2005
Simvastatin	40 mg	2004
Acetylsalicylic acid	100 mg	2004
Clopidogrel	75 mg	2005
Digitoxin	0.07 mg	August 2006

Since mid-September 2006 he developed fatigue, weakness and muscle pain. His urine turned dark, then frankly brown, and he was admitted to our hospital. On examination, his muscles were tender and very weak. Laboratory tests (see Table 2) showed rhabdomyolysis with CK elevation about 50-fold above the normal range (9,186 U/l). Myoglobin levels were greatly elevated. Creatinine levels were elevated at 2.9 mg/dl. Amiodarone and digitoxin levels were within the therapeutic range. After discontinuation of simvastatin and adequate hydration for several days CK levels dropped and creatinine improved to 1.9 mg/dl. Digitoxin therapy was continued. Clinically, after 2 weeks he regained muscular strength and was pain free. CK levels were completely normalized.

DISCUSSION AND CONCLUSION

This patient with heart failure and underlying mild renal insufficiency had severe rhabdomyolysis and worsening renal failure

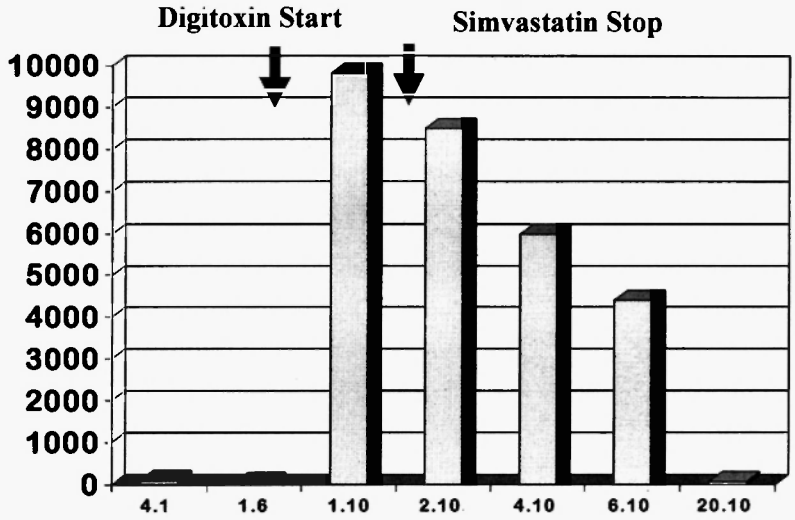

Fig. 1: Year 2006 time course of creatine kinase levels.

when digitoxin was added to a stable therapeutic regimen for congestive heart failure that included simvastatin as well as amiodarone. Luckily he had a rapid and full recovery and improvement of renal function after discontinuation of the statin and fluid administration.

This case is unique firstly in that it shows that rhabdomyolysis can be induced by addition of a risk factor (digitoxin) even after years of uneventful statin therapy. Secondly, even though several reports have described statin-induced rhabdomyolysis under digoxin co-therapy /4/, to our knowledge this is the first report describing this side effect for digitoxin. One mechanism may be interference of digitoxin with P-glycoprotein-mediated drug transport /6/. Furthermore, it is well known that amiodarone and statins both inhibit cytochrome P450 activity /7/. This second drug-drug interaction may have been balanced until the addition of digitoxin, ultimately leading to muscular damage by increasing statin concentrations. Unfortunately, serum simvastatin levels were not measured. As a third risk factor the patient had mild underlying renal failure possibly reducing his overall drug clearance.

For clinical practice, it can be concluded that creatine kinase levels should be tested not only after initiation of statin therapy but also after

TABLE 2

Patient's laboratory values at time of admission and discharge

	Admission	Discharge	Reference
Creatine kinase (U/l)	9,186	4,027	<190
CK-MM	8,561	–	
CK-MB	92	–	
CK-BB	0	–	
Macro-CK type 1	553	–	
Macro-CK type 2	0	–	
Myoglobin (μg/l)	9049	–	28-72
Aspartate transaminase (U/l)	276	180	0-50
Alanine transaminase (U/l)	216	208	0-50
Lactatdehyrogenase (U/l)	315	316	0-250
Creatinine (mg/dl)	2.9	1.9	0.7-1.5
Total cholesterol (mg/dl)	128		0-200
Amiodarone (mg/l)	1.4		
Desethylamiodarone (mg/l)	0.3		
Digitoxin (ng/ml)	25.9		10-30

addition of new drugs with possible interactions. In patients with heart failure receiving a drug 'cocktail', digoxin, digitoxin and amiodarone co-therapy in particular should be critically observed. Clinicians should be aware of the possibility of rhabdomyolysis and should instruct patients to watch for symptoms of myopathy, which should prompt an immediate consultation with their physician.

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