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CASE REPORT

Rosuvastatin and Colchicine combined myotoxicity: lessons to be learnt

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Abstract

Statins and colchicine co-administration consists of a potentially catastrophic drug–drug interaction since it provokes myotoxicity, myopathy and various degrees of rhabdomyolysis. Lipophilic statins and colchicine are biotransformed in the liver, primarily via CYP3A4 enzyme system leading to elevated blood levels of both agents and resulting in increased potential for combined myotoxicity. Hence, it would be of great clinical importance not only the awareness of this devastating complication but also the more advantageous type of statin that we should choose to achieve the recommended therapeutic goals regarding LDL levels with minimal myopathy risk. Therefore, once colchicine's use is commenced, a hydrophilic statin selection, such as rosuvastatin, seems favorable regarding the risk of myotoxicity. Herein, we aim to describe a patient with chronic kidney disease stage III and nephrotic syndrome that developed acute rhabdomyolysis soon after the administration of rosuvastatin while receiving colchicine. To the best of our knowledge, this is the first report of the combined effect of rosuvastatin and colchicine in the setting of chronic kidney disease leading to myotoxicity.

Introduction

Drug–drug interactions consist of one of the most well-known risk factors correlated with statin-associated myopathy (SAM) [1]. Statins and colchicine co-administration has also been reported as a potentially devastating drug–drug interaction that provokes myotoxicity and includes clinically muscle cramps, generalized weakness, various degrees of muscle pain, signs of myositis and rhabdomyolysis [2, 3]. Interestingly, colchicine was identified as the second most common drug interaction in patients receiving simvastatin [4].

In most cases, the increased risk of myopathy when combined therapy is applied has been associated with the fact that both lipophilic statins and colchicine are biotransformed in the liver, primarily via CYP3A4 enzyme system [5]. On the contrary, the hydrophilic class of statins, which are not metabolized by cytochrome P450 isoenzymes, when co-administrated with colchicine, may provoke myotoxicity through the metabolic pathway of P-glycoprotein transporter [6, 7].

Accordingly, a drug–drug interaction between rosuvastatin and colchicine cannot be explained on the basis of the above pathophysiological mechanisms, since rosuvastatin neither undergoes metabolism through CYP3A4 enzyme system nor transports following the P-glycoprotein pathway [8]. Herein, our reported case of severe rhabdomyolysis after concomitant use of colchicine and rosuvastatin in a nephrotic patient could be plausibly attributed to the combined myotoxic effects of both drugs. To the best of our knowledge, this is the first reported case in the literature of this noxious interaction, despite the fact that both drugs independently are well-known myotoxins.

Case presentation

A 49-year-old male presented in the emergency department complaining of a 1-week history of generalized fatigue and progressive muscle pain in both thighs and calves. He also noted the presence of tea-colored urine accompanied with a urine volume decrease. There was no associated fever, skin rash, influenza-like symptoms or any preceding history of

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vigorous physical activity. His medical history included chronic kidney disease stage III due to IgA nephropathy, ischemic heart disease, diabetes mellitus induced by long-lasting corticosteroid therapy, resistant hypertension and uncontrolled dyslipidemia attributable to heavy proteinuria.

More specifically, the patient had been subjected to renal biopsy 7 years ago because of renal impairment (serum creatinine 1.6 mg/dL), accelerated hypertension, nephrotic-range proteinuria (total urine protein 5110 mg/24 h) and gross hematuria associated with the upper respiratory tract infection. Histopathological microscopy study in seventeen glomeruli revealed moderate mesangiopathic lesions with focal and segmental distribution including expansion of the mesangial matrix, moderate proliferation of mesangial cells accompanied with significant findings of possible secondary focal segmental glomerulosclerosis. Nine out of seventeen (nearly 53%) glomeruli presented globally or segmentally glomerulosclerotic whereas the extend of chronic tubulointerstitial fibrotic area was 30–35%. Immunofluorescent microscopy study showed predominantly staining for IgA (++) with no evidence of IgG, IgM and C1q deposits. The absence of IgM and C3 deposits in the sclerotic areas excluded the possibility of IgA nephropathy and focal segmental glomerulosclesoris (FSGS) coexistence.

Afterwards, the patient received combined immunosuppressive therapy with corticosteroids and alkylating agents along with conservative therapy including irbesartan and omega-3 fatty acid supplements. Of note, immunosuppressant therapy with corticosteroids had been ceased 1 year ago, once the diagnosis of extrapulmonary tuberculous lymphadenitis had been made.

Concerning his lipid-lowering therapy, the patient had been commenced on atorvastatin 20 mg/day for the past 4 years with a recent change by his cardiologist to rosuvastatin 40 mg/day plus ezetimibe 10 mg/day, 10 days prior to the onset of symptoms, due to poor lipid control (Table 1). Of interest, the patient had no history of muscular toxicity with atorvastatin. Moreover, there was a recent history of 1-month administration of colchicine 0.5 mg twice daily due to an episode of acute pericarditis that had been thoroughly investigated and revealed no secondary causes. The patient was treated on regular basis with metoprolol, torasemide, irbesartan, amlodipine, moxonidine, aspirin and a mixture of an intermediate-acting human insulin analog with a rapid-acting human insulin analog. He did not report any illicit drug or alcohol use. He denied also any gastrointestinal symptoms indicating colchicine intoxication.

On physical examination, he was afebrile but demonstrated extreme symmetric proximal weakness and significant muscle tenderness in both lower extremities, without gross neurological deficits. Pulse rate was 76/min and blood pressure 100/65 mmHg. In the respiratory and cardiovascular system, there were no abnormal findings. He had moderate palpable pedal edema. Laboratory studies revealed elevated levels of creatine kinase (21.000 U/L), aspartate aminotransferase (645 U/L), alanine aminotransferase (689 U/L), lactate dehydrogenase (930 U/L), worsening renal function with creatinine level of 5.2 mg/dL, serum albumin level of 2.1 g/L, anemia with hemoglobin levels of 10.1 g/dL and moderate hyperphosphatemia (6.8 mg/dL). No other electrolyte abnormalities were observed apart from mild hypocalcaemia (8.1 mg/dL corrected to albumin). Patient's Laboratory Data before and 10 days after rosuvastatin administration are recorded in Table 1.

Afterwards, the patient was hospitalized with the diagnosis of rahbdomyolysis likely induced by concomitant use of rosuvastatin and colchicine. The offensive drugs were discontinued immediately as well as toresemide and other antihypertensive drugs and the patient received isotonic crystalloid solutions on the basis of regular blood pressure and urine output monitoring, to restore intravascular volume. Alkaline therapy was also implemented during the first 3 days of hospitalization, targeting an alkaline urine pH of greater than 6.5 to attenuate the toxicity of myoglobin to the tubular epithelial cells. Over the next 7 days, the patient's renal function returned to baseline levels (serum creatinine 2.7 mg/dL) and other muscle-related enzyme levels began gradually to stabilize to normal values. On the 7th day of hospitalization, the patient discharged home and sustained stable regarding creatinine levels on 1-month follow-up (Fig. 1).

Discussion

Colchicine is a well-known anti-inflammatory drug since antiquity, that seems to exert pleiotropic properties still undetermined but possibly attributable to intricate immunoregulatory and immunosuppressive actions. Currently, colchicine is widely used for the treatment of several inflammatory diseases beyond its predominant indication for gout management [9]. Long-lasting colchicine use is considered to be a safe and well-tolerated therapeutic option, since neuro- and myotoxicity or even rhabdomyolysis are dose-dependent adverse effects, presenting usually after months or years of colchicine administration [10].

However, there are recently available data regarding the potentially fulminant onset of muscular symptoms associated with the concurrent administration of colchicine and statins. A growing number of patients on combination therapy have already been reported to present with severe neuromuscular toxicity and rhabdomyolysis which in some cases are accompanied by myoglobin-induced acute renal injury [3]. Similar to colchicine, statins are also well-known myotoxins primarily in patients with distinct characteristics including advanced age, low body mass index, female

Table 1 Patient's laboratory data

Laboratory examination	Normal ranges	1 month before rosuvastatin administration	On admittance
Hct (%)	40–52	**38.6**	**34.1**
Hb (g/dL)	13–17.5	**12.8**	**10.1**
WBC (10^3/μL)[a]	4.2–10.8	6.49	**12.35**
Neu (%)	40–75	47.9	62.4
Lym (%)	20–45	43.5	29.6
CRP (mg/dL)[a]	0.1–0.5	0.1	**3.8**
ESR (mm/h)[a]	0–15	**46**	**80**
Urea (mg/dL)	13–50	**60**	**248**
Creatinine (mg/dL)	0.6–1.3	**2.5**	**5.2**
Total cholesterol (mg/dL)	130–200	**265.3**	**155.6**
HDL (mg/dL)[a]	> 40	**37**	**35**
LDL (mg/dL)[a]	< 130	**162.3**	91.8
TRIG (mg/dL)[a]	50–150	**230**	140
Albumine (g/L)	3.4–4.8	**2.8**	**2.1**
AST (U/L)[a]	14–40	27	**645**
ALT (U/L)[a]	15–38	24	**689**
CPK (U/L)[a]	26–192	122	**21.000**
LDH (U/L)[a]	135–225	138	**930**
K (mmol/L)	3.5–5.1	4.5	**5.3**
Na (mmol/L)	135–147	138	140
Ca (mg/dL)	8.5–10.2	9.2	**8.1**[(1)]
P (mg/dL)	2.4–4.6	3.5	**6.8**
TSH (μIU/mL)[a]	0.27–4.2	1.46	1.49
Total protein in urine (mg/24 h)	40–150	6320	(–)
Urine sediment			
Oval fat bodies	–	+++	+
Cholesterol crystals	–	+++	+
Renal tubular epithelial cells	–	–	+++
"Muddy brown" casts	–	–	++
RBCs of glomerular origin/HPF	–	*5–10*	*5–10*

Bold values represent pathologic values

italic values represent abbreviations

[a]*WBC* white blood cells, *RBC* red blood cells, *CRP* C-reactive protein, *ESR* erythrocytre sendimentation rate, *HDL* high-density lipoprotein, *LDL* low-density lipoprotein, *TRIG* Triglycerides, *AST* aspartate aminotransferase, *ALT* alanine aminotransferase, *TSH* thyroid stimulate hormone, *HPF* high-power field

[(1)]Corrected to albumin

gender, diabetes mellitus, hypothyroidism, chronic kidney disease and impaired liver function [11]. Hence, different types of statins have been reported to incite severe rhabdomyolysis when co-administrated with colchicine, such as simvastatin [12], atorvastatin [13], fluvastatin [14] and pravastatin [6].

Moreover, it has long been considered that lipophilic statins (simvastatin, atorvastatin) are more likely to exert myotoxicity than their hydrophilic counterparts (pravastatin, rosuvastatin, fluvastatin) [15]. Lipophilic statins are metabolized by the hepatic cytochrome P450 3A4 (CYP3A4) enzyme system, whereas hydrophilic statins do not depend on CYP3A4. Additionally, a significant portion of colchicine is metabolized by the CYP3A4 enzyme system. Therefore, simultaneous use of colchicine with CYP3A4 inhibitors/competitors—such as lipophilic statins—can lead to elevated blood levels of both agents, resulting in increased potential for combined myotoxicity. In our case, the above drug-drug interaction did not happen during co-medicated therapy with colchicine and atorvastatin. This can be explained by the fact that colchicine is predominantly eliminated through transport by P-glycoprotein, which orchestrates the colchicine biliary, renal and gout excretion [16]. Thus, once colchicine's use is commenced, a hydrophilic statin selection seems advantageous regarding the risk of myotoxicity. However, in our patient this option turned out to be

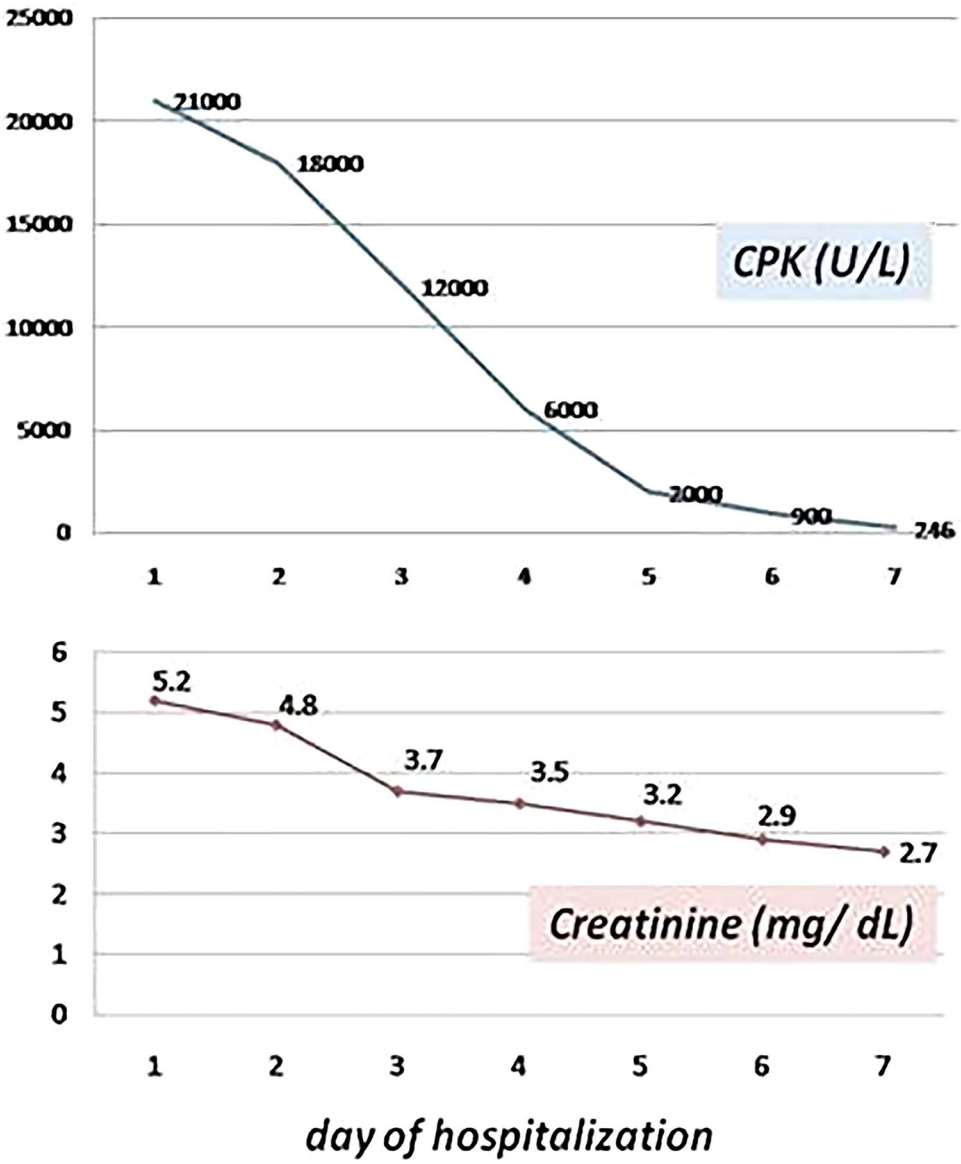

Fig. 1 Fluctuation of CPK and creatinine levels during patient's hospitalization

detrimental. Concerning rosuvastatin, it is well-known that it neither undergoes metabolism via the cytochrome P450 nor transports through P-glycoprotein. Rosuvastatin is eliminated from the bloodstream, principally by the organic anion transporter protein OATP-C and consequently a drug–drug interaction could only be explained by an aberrant transporter-mediated mechanism [8].

Taking into account the above, it seems possible that rhabdomyolysis was the combined result, possibly additive or even more synergistic, of two certain myotoxins in a vulnerable patient (Fig. 2).

First, the temporal correlation between initiation of symptoms and concurrent exposure to both drugs was approximately 10 days. Indeed, reported cases of patients receiving statins co-medicated with colchicine, describe the onset of muscular symptoms ranging from 8 to 20 days [12]. Second, since both drugs were not commenced concomitantly, one may consider that rhabdomyolysis was simply a statin-associated side effect and not a drug-drug interaction. Certainly, our patient received the maximum dose of rosuvastatin that is contraindicated in patients with moderate renal impairment [17]. Of note, the patient had no previous history of statin-associated muscle symptoms despite the fact that he was receiving atorvastatin for a long period. According to Naranjo Adverse Drug Reaction Probability Scale, rosuvastatin was illustrated as "probable" cause of rhabdomyolysis (score 7), even if alternative causes such as an additive reaction with colchicine should also be considered [18].

Furthermore, it is important to underline that, in patients with severe secondary dyslipidemia caused by nephrotic syndrome, the use of statins has been less well-studied. A meta-analysis that included four randomized controlled

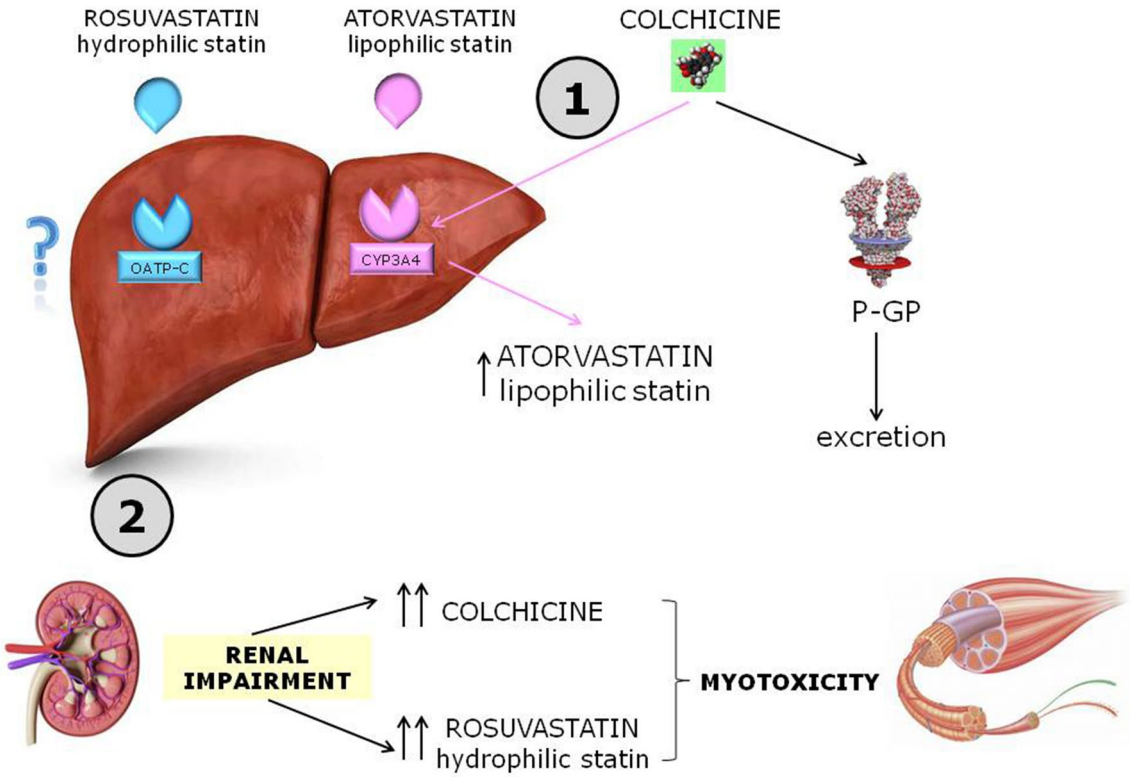

Fig. 2 Simultaneous use of colchicine with CYP3A4 inhibitors (atorvastatin) can lead to elevated blood levels of both agents. Colchicine is predominantly eliminated through transport by P-glycoprotein (expressed in both liver and kidney). Rosuvastatin is eliminated principally by the organic anion transporter protein OATP-C. Consequently, combined myotoxicity could be explained by an aberrant transporter-mediated mechanism in this nephrotic patient

studies revealed limited statins' effectiveness and this may be correlated with significant changes regarding bioavailability [19]. Hence, since the volume of distribution of rosuvastatin is nearly 134 L in steady state and approximately 90% is bound to plasma proteins (mainly albumin) [20], it seems reasonable that in our patient, who suffered from nephrotic syndrome, dramatic changes in these parameters could exist. The implication of nephrotic syndrome regarding altered pharmacokinetic and pharmacodynamic of rosuvastatin remains elusive. Ones may argue that high urinary protein loss translates to accumulation of the free drug and increased myotoxicity risk and conversely, another that protein-bound rosuvastatin is promptly lost in the urine, reducing potency.

Taken together the above, it seems rational that in the case of a highly protein-bound drug such as rosuvastatin the percentage of free drug is increased significantly alongside with a lower steady-state concentration due to enhanced clearance following a counterbalanced pattern. Therefore, the myotoxic effects of rosuvastatin in a nephrotic patient such as ours, may not be predictable, particularly if other factors such as oral bioavailability, no dose adjustment to glomerular filtration rate, alterations of distribution volume and synergistic effects of other drugs are taken into account.

It also seems reasonable, that the severe deterioration of renal function in our patient was accelerated by the concomitant use of irbesartan and torasemide in an already hypovolemic nephrotic patient. In favor of the above, the presence of renal tubular epithelial cells in urine sediment examination suggests the critical role of hypovolemia and prerenal azothemia in acute renal injury whereas explains satisfactorily the rapid improvement of kidney function after discontinuation of all offensive drugs and restoration of active blood volume.

As regards the additive role of colchicine, it may be explained by the fact that myotoxic effects of this agent usually occur when renal excretion is impaired, resulting in prolonged terminal elimination up to two- to threefold. This is certainly true in our case alongside the occurrence of hypoalbuminemia that possibly changed the apparent volume of drug distribution and consequently the potential of tissue binding [16]. The above is exemplified in the work undertaken by Akayasu and colleagues, in a fluvastatin-treated patient who developed rhabdomyolysis after short-term intake of colchicine. The authors argue that fluvastatin and colchicine co-administration exert synergistic myotoxicity actions via pharmacokinetic and pharmacodynamic

mechanisms [14]. In a similar case of a patient with chronic kidney disease who developed severe rhabdomyolysis after combined exposure to simvastatin and colchicine, Baker and colleagues proposed that synergistic cytoskeletal myotoxicity includes the colchicine induced-myopathy through disruption of microtubular function with subsequent vacuolization as well as the statins-associated disruption of cytoskeletal integrity [21].

In conclusion, concomitant use of colchicine and rosuvastatin seems to be a potential risk factor for myotoxicity and rhabdomyolysis since both drugs exert potent myotoxic properties in the setting of chronic renal impairment. It is therefore of paramount clinical importance the knowledge of this potentially devastating drug-drug interaction as well as "which statin" and at "what dose" should be prescribed during combination therapy with colchicine.

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