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CASE REPORT

Colchicine-Induced Acute Neuromyopathy in a Patient Using Concomitant Fluconazole: Case Report and Literature Review

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Abstract A 54-year-old woman presented at the emergency department after experiencing lower limb weakness and bilateral ankle pain for 2 days. She had a history of type 2 diabetes mellitus, diabetes mellitus nephropathy with chronic kidney disease, and chronic gouty arthritis. She had received 0.6 mg colchicine orally once or twice daily for 8 months. Four days prior to her emergency department visit, she was discharged from our nephrology ward, where she had been admitted because of a urinary tract infection. During hospitalization, she was treated with intravenous cefazolin for 7 days. Because of persistent symptoms, we performed repeated urinalysis, which revealed the presence of yeast. She was diagnosed with fungal cystitis, and was administered a 7-day course of once-daily oral fluconazole (100 mg). On day 5 of the course, she was discharged and asked to continue taking oral colchicine (0.6 mg, twice daily), as well as fluconazole for the full 7-day course. Neurological examination revealed marked symmetrical weakness (Medical Research Council grade 4/5). Her sensation and coordination were intact. Initial laboratory investigation revealed hyperkalemia (6.2 mmol/L), and blood urea nitrogen, serum creatinine, and creatine kinase levels of 181, 11.16 mg/dL, and 803 U/L respectively. Her liver function tests showed elevated alanine aminotransferase levels (112 U/L). Electromyographic results were consistent with colchicine neuromyopathy. Ten days after treatment cessation, muscle enzyme levels normalized and weakness gradually disappeared. We used the Drug Interaction Probability Scale to evaluate our patient's case. A score of 5 was calculated, indicating that the drug–drug interaction was the probable cause of neuromuscular toxicity.

Key Points

The widespread use of colchicine may expose a large population to potential risk, especially patients with impaired renal function undergoing combination drug therapies that share common metabolic pathways.

Clinicians should be cautious when co-administering colchicine with other drugs, especially in patients with impaired renal function.

Serious neuromuscular adverse events could occur with the concurrent use of colchicine and fluconazole.

Introduction

Colchicine is an ancient therapeutic used to treat gouty arthritis [1]. Although its clinical benefits are well documented, colchicine has been associated with adverse effects secondary to drug–drug interactions. The probable mechanisms of colchicine-induced adverse events include the

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deterioration of renal function and cytochrome P450 (CYP) 3A4 inhibition, leading to poor drug clearance and increased serum concentrations [2]. Some antibiotic- and cholesterol-lowering drug-related interactions have been reported. Fluconazole is a triazole antifungal agent that inhibits CYP2C19 (strong inhibition), CYP2C9 (moderate inhibition), and CYP3A4 (moderate inhibition) [3]. This is the first reported case of neuromyopathy induced by administration of fluconazole to a patient undergoing long-term colchicine therapy.

Case Report

A 54-year-old woman presented to the emergency department after 2 days of lower limb weakness and bilateral ankle pain. She had a known history of type 2 diabetes mellitus, diabetes mellitus nephropathy with chronic kidney disease, and chronic gouty arthritis. She was orally administered 0.6 mg colchicine once or twice daily for 8 months. She reported no recent traumatic event, alcohol ingestion, or substance abuse.

Four days before visiting our emergency department, the patient was discharged from our nephrology ward after undergoing treatment for a urinary tract infection. During her hospitalization, she was administered intravenous cefazolin for 7 days. Her current maintenance medications including oral colchicine (0.9 mg, once daily) were also prescribed. She still experienced dysuria, urgency, and lower abdominal fullness. Repeated urinalysis revealed the presence of yeast. She was diagnosed with fungal cystitis and administered a 7-day course of oral fluconazole (100 mg) once daily. On day 5 of the course, she was discharged and asked to continue treatment with oral colchicine (0.6 mg, twice daily) and fluconazole to complete the 7-day course.

The initial physical examination revealed an arterial blood pressure of 133/69 mmHg, a pulse rate of 89 beats/min, a respiratory rate of 19 breaths/min, and body temperature of 36.6 °C. She had bilateral tenderness in her ankles with general weakness. Neurological examination revealed marked symmetrical weakness (Medical Research Council grade 4/5). Her sensation and coordination were intact. She had no rash or lymphadenopathy. Her chest plain film showed no active lung lesion and borderline heart size. Cardiac echography revealed preserved left ventricle systolic function without cardiac chamber dilatation. Initial laboratory investigations revealed hyperkalemia (6.2 mmol/L vs. normal: 3.4–4.7 mmol/L), and elevated blood urea nitrogen (181 mg/dL vs. normal: 7–20 mg/dL), serum creatinine (11.16 mg/dL vs. normal: 0.5–1.2 mg/dL), and creatine kinase (CK, 803 U/L vs. normal: 24–120 U/L) levels. Her liver function tests showed elevated alanine aminotransferase (ALT, 112 U/L vs. normal: 0–40 U/L) levels. She had a decreased white blood cell count (2830 cells/mL vs. normal: 4000–9900 cells/mL) and hemoglobin levels (9.7 g/dL vs. normal: 12–16 g/dL). Anemia, indicated by the reduced hemoglobin level, is a common complication of chronic kidney disease. Cholesterol levels, amylase, direct and indirect bilirubin, C-reactive protein, rheumatoid factor, and thyroid hormones were all within their normal ranges.

Motor nerve conduction studies revealed prolonged distal latency, slow nerve conduction velocity, delayed F-wave latency on four limbs, and low compound muscle action potential amplitude in the bilateral peroneal and tibial nerves. Hoffmann's reflex study showed no response in both lower limbs. Sensory nerve conduction studies revealed slow nerve conduction velocities in bilateral median nerves across the wrist, and relatively low sensory nerve action potential amplitude in four limbs. Needle electromyography demonstrated severely active denervation in both the lower limbs.

She was diagnosed with neuromyopathy based on clinical presentation and laboratory studies. On admission, her anti-inflammatory drugs were changed to corticosteroids for gouty arthritis, and colchicine was withdrawn. Ten days after the cessation of colchicine, her laboratory values returned to the normal range (potassium 4.1 mmol/L; ALT 41 U/L; white blood cell count 5540 cells/mL), with the exception of the hemoglobin level (9.6 g/dL). Her weakness disappeared gradually.

Discussion

We searched the PubMed electronic database for literature from 1987 to 2013, using the keywords colchicine, myopathy, neuromyopathy, rhabdomyolysis, and myotoxicity. We limited the search to case reports published in English involving adult patients. We identified 114 articles in which colchicine-induced neuromyopathy was reported. Both authors scanned titles and abstracts for initial selections. Forty-three articles were not associated with drug interactions, and were therefore excluded. Fifty-one articles were excluded because the mentioned drug–drug interactions were not related to myopathy. Finally, we extracted the following data from 20 articles describing 24 different cases (Table 1) [4–23]: baseline demographic characteristics (age, sex); colchicine dose and duration of use; recent concomitant drug dose; symptom presentation after concurrent drug use; time from concomitant drug dose to symptoms; CK, aspartate transaminase (AST), and ALT levels, electromyography findings; and time to resolution.

The mean age of the patients who experienced drug interaction-induced myopathy was 58 ± 15 years, 83 %

Table 1 Characteristics of included case reports

Study, year	Age (years)	Sex	Length of colchicine Therapy	Dose/day (mg)	Co-administered agents	Presenting symptoms	Time from first concurrent drug dose to symptoms (days)	Laboratory data		Time to resolution
								CK (U/L)	AST/ALT (U/L)	
Mckinnell et al., 2009 [4]	48	M	Long-term use	0.6	Clarithromycin	Severe muscle pain	3	22,996	513/182	4 days
van der Velden et al., 2008 [5]	73	M	1 year	0.5	Clarithromycin	Muscle weakness, fatigue	10	1396	219/345	14 days
Alayli et al., 2005 [6]	65	F	NR	1.5	Pravastatin	Proximal muscle weakness	20	914	149/120	7 days
Bouquié et al., 2011 [7]	34	M	8 days	Day 1: 3 mg Day 2–3: 2 mg Day4–8: 1 mg	Pravastatin Azithromycin Cyclosporine	Multiple organ failure rhabdomyolysis	8	3206	122/136	11 days
Hsu et al., 2002 [8]	70	F	NR	1	Simvastatin	Proximal muscle weakness	14	918	AST:107	14 days
Oh et al., 2012 [9]	84	M	NR	1 mg qd for 3 days, then 0.5 mg qd	Simvastatin	Proximal muscle weakness	21	2837	NR	56 days
Francis et al., 2008 [10]	66	M	NR	1.2	Simvastatin	Muscle weakness	NR	2538	NR	
Baker et al., 2004 [11]	79	M	NR	1.2	Simvastatin	Severe muscle proximal weakness	8	32,040	NR	14 days
Justiniano et al., 2007 [12]	61	F	NR	1.2	Simvastatin	Muscle weakness	12	6765	NR	14 days
Sahin et al., 2008 [13]	30	M	Long-term use	1.5	Simvastatin	Muscle pain, proximal muscle weakness and cramps	21	1232	67/71	14 days
Atasoyu et al., 2005 [14]	70	M	NR	1.5	Fluvastatin	Arms and legs weakness, severe pains	3	37782	AST:856	19 days
Sarullo et al., 2010 [15]	77	M	NR	1	Fluvastatin	Arms pain, legs weakness	14	2371	617/523	16 days
Atmaca et al., 2002 [16]	40	M	3 years	1.5	Gemfibrozil	Muscle pain	14	3559	232/165	9 days
Tufan et al., 2006 [17]	45	M	3 years	1.5	Atorvastatin	Lower extremity weakness, muscle pain, gait instability	14	9035	513/72	10 days
Sahin et al., 2008 [13]	43	M	2 months	1.5	Atorvastatin	Muscle pain and proximal muscle weakness	14	608	38/24	21 days
Sahin et al., 2008 [13]	30	M	Long-term use	1	Atorvastatin	Muscle pain and proximal muscle weakness	20	11,069	342/347	7 days
Torgovnick et al, 2006 [18]	74	M	NR	NR	Lovastatin	Proximal muscle weakness	28	8370	NR	Several weeks
Lee et al., 1997 [19]	49	M	NR	2.4	Cyclosporine	Mild muscle weakness in the lower extremities	3	14958	561/403	14 days

Table 1 continued

Study, year	Age (years)	Sex	Length of colchicine Therapy	Dose/day (mg)	Co-administered agents	Presenting symptoms	Time from first concurrent drug dose to symptoms (days)	Laboratory data		Time to resolution
								CK (U/L)	AST/ALT (U/L)	
Gruberg et al., 1999 [20]	53	M	NR	1.5	Cyclosporine	Muscle pain and weakness	NR	3003	141/90	14 days
Eleftheriou et al., 2008 [21]	60	M	NR	1	Cyclosporine	Myalgia, vomiting, diarrhea	6	658	775/376	27 days
Garrouste et al., 2012 [22]	59	M	7 days	3	Cyclosporine	Abdominal pain with mucous diarrhea Myalgia	5	4116	166/105	30 days
Rana et al., 1997 [23]	53	M	6 months	0.6	Cyclosporine	Proximal weakness	NR	>3000	NR	7 days
Rana et al., 1997 [23]	56	M	NR	NR	Cyclosporine	Malaise, fatigue, generalized weakness	NR	449	NR	A few weeks
Rana et al., 1997 [23]	57	F	NR	NR	Cyclosporine	Generalized weakness, distal extremity paresthesia	NR	721	NR	30 days

ALT alanine aminotransferase, *AST* aspartate aminotransferase, *CK* creatine kinase, *F* female, *M* male, *NR* not reported

were men, and most had underlying comorbidities (chronic kidney disease, dyslipidemia, or solid organ transplantation). The duration of concomitant drug use with colchicine therapy ranged from 3 to 28 days (mean ± standard deviation, 13 ± 7 days), with a mean cumulative daily dose of 1.27 ± 0.6 mg. The mean time to resolution after drug discontinuation was 17 ± 12 days. Most patients in this case series presented with proximal muscle weakness. As in our report, CK, ALT, and AST levels were significantly elevated. Hyperkalemia is caused by the release of potassium from damaged myocytes. The blood potassium level may increase rapidly, but it decreases as it is eliminated in the urine. Elevated levels of AST and ALT may be caused by hepatic inflammation, which occurs in approximately 25 % of patients with rhabdomyolysis or myopathy. The possible mechanism for this inflammation is related to the proteases released from the injured muscle [24].

Colchicine is primarily cleared from the body via bile, the intestinal tract and, to a lesser extent, renal excretion. In one study in normal healthy subjects, 14–40 % of the unchanged drug and 4–14 % of its metabolites were recovered in the urine [25]. The impaired renal function in the present case was a risk factor for colchicine toxicity, but not the primary mechanism, as she had been orally administered 0.6 mg colchicine one to two times daily for 8 months prior to this event. Previous reports have suggested that numerous drugs, including clarithromycin, pravastatin, simvastatin, fluvastatin, atorvastatin, gemfibrozil, and cyclosporine, contribute to neuromyopathy associated with drug–drug interactions following colchicine administration. The possible mechanisms of interaction were inhibited demethylation of colchicine in the liver before excretion, which is dependent on CYP3A4, concurrent administration of CYP3A4 substrates, and interference with P-glycoprotein-mediated transport [26]. Co-administration of these drugs impairs the metabolism of colchicine, which leads to decreased colchicine clearance, and increased plasma colchicine concentrations. The high plasma concentrations may have also caused myelosuppression and leukopenia in two reported cases [27]. Furthermore, co-administration can impair axonal transport in peripheral nerves, thereby altering the microtubule-dependent cytoskeleton necessary for the normal lysosome movement in cells [28]. To our knowledge, this is the first case of neuromyopathy induced by concomitant use of colchicine and fluconazole. We have used the Drug Interaction Probability Scale to evaluate our patient's case [29]. A score of 5 was calculated, indicating that the drug–drug interaction was the probable cause of neuromuscular toxicity. Based on the well-documented pharmacokinetic mechanism and similar drug interactions with other CYP3A4 substrates or inhibitors, it is strongly suspected that a drug–drug interaction induced the neuromyopathy.

Conclusion

We presented a case of a patient who developed neuromyopathy secondary to concomitant use of colchicine and fluconazole. The use of colchicine in the treatment of gouty arthritis may be associated with neuromuscular adverse events. The widespread use of this medication may expose a large population to potential risk, especially patients with impaired renal function undergoing combination drug therapies that share common metabolic pathways. Physicians should be cautious when co-administering colchicine with other drugs, and carefully monitor patients for symptoms of myotoxicity.

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