Kidney Res Clin Pract 32 (2013) 74–77

Kidney Research and Clinical Practice

journal homepage: http://www.krcp-ksn.com
Contents lists available at ScienceDirect

Case Report

Colchicine-induced myoneuropathy in a cyclosporine-treated renal transplant recipient

Kyungmin Huh [1], Ji Young Joung [1], Hyemin Jeong [1], Dongmo Je [1], Yoon Young Cho [1], Hye Ryoun Jang [2], Wooseong Huh [2,*]

[1] Department of Internal Medicine, Samsung Medical Center, Sungkyunkwan University School of Medicine, Seoul, South Korea
[2] Division of Nephrology, Samsung Medical Center, Sungkyunkwan University School of Medicine, Seoul, South Korea

ARTICLE INFO

Article history:
Received 14 May 2012
Received in revised form
20 July 2012
Accepted 7 August 2012
Available online 23 May 2013

Keywords:
Colchicine
Cyclosporine
Gout
Myoneuropathy
Renal transplant

ABSTRACT

Colchicine is a relatively safe medication that is widely used for both prevention and treatment of gout attack. However, serious adverse events, including myoneuropathy and multiorgan failure, have been reported. We report a case of colchicine-induced myoneuropathy in a female kidney transplant recipient who had been taking cyclosporine. She developed gastrointestinal discomfort and paresthesia 5 days after the initiation of colchicine. She showed signs of myoneuropathy, and hepatic and renal injury. Colchicine toxicity was suspected, and colchicine was discontinued. Her symptoms and laboratory findings improved gradually. Literature was reviewed for previous reports of colchicine-induced myoneuropathy in solid organ transplant recipients.

Introduction

Gout is common in organ transplant recipients as a consequence of cyclosporine therapy, and impaired renal function acts as another predisposing factor in renal transplant recipients [1]. As nonsteroidal anti-inflammatory drugs (NSAIDs) are potentially nephrotoxic, colchicine is used frequently for both treatment and prevention of acute gout attack. Although colchicine is a relatively safe medication, it has been reported to be toxic. Gastrointestinal symptoms are common symptoms of colchicine toxicity; however, more severe adverse events such as myoneuropathy [2] and multiorgan failure [3] have also been reported. Cyclosporine is used widely as an immunosuppressant in organ transplant recipients. A number of case reports of colchicine toxicity associated with concomitant use of cyclosporine have been published [3–11], but they vary depending on the symptoms, dose, and duration of medication; the affected organs; and outcomes. Here, we report another case of myoneuropathy and multiple organ involvement associated with concomitant use of colchicine and cyclosporine in a renal transplant recipient, and review the previous case reports.

Case report

A 57-year-old female, with diabetes, hypertension, and a history of kidney transplantation 13 years ago from a deceased donor, was admitted due to epigastric pain and poor oral intake. She maintained normal renal function for 10 years, but her estimated glomerular filtration rate started to fluctuate 3 years prior to admission. Her serum creatinine was stabilized at 1.65 mg/dL about 2 years ago and was maintained in the range of 1.4–1.6 mg/dL thereafter. The patient developed the first acute gout attack on her left ankle 2 years ago, and was started on prednisolone 10 mg twice a day and allopurinol 100 mg once a day. After 1 month, prednisolone was tapered off gradually, but the aggravation of gout about 2 months prior to admission

* Corresponding author. Division of Nephrology, Samsung Medical Center, Sungkyunkwan University School of Medicine, Seoul 135-710, South Korea.
E-mail address: wooseong.huh@samsung.com (W Huh).

2211-9132/$ - see front matter © 2013. The Korean Society of Nephrology. Published by Elsevier. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).
http://dx.doi.org/10.1016/j.krcp.2013.04.003

required readministration of prednisolone. For control of hyperglycemia, prednisolone was substituted by colchicine 0.3 mg twice a day about 3 weeks prior to admission. The patient had been taking deflazacort 3 mg once a day, cyclosporine 50 mg twice a day, and mycophenolate 500 mg twice a day. She was also taking rosuvastatin 20 mg once a day, which had been used since January 2009 without any side effects. Five days after starting colchicine, she developed epigastric pain with nausea and vomiting. She began to complain of tingling sensation and numbness on the plantar area of both feet and the radial side of both hands 2 days later. After 21 days on colchicine, she visited the emergency department of our center. On initial presentation, physical examination revealed no abnormal finding, except mild dehydration. Sensory function of affected limbs was normal, and she did not show any signs of motor weakness. The complete blood count showed white blood cell count of 8,770/μL, hemoglobin level of 15.8 g/dL, and platelet count of 198,000/μL. Chemistry profiles were as follows: total bilirubin 1.5 mg/dL, aspartate transaminase 166 U/L, alanine transaminase 118 U/L, alkaline phosphatase 77 U/L, blood urea nitrogen 26.4 mg/dL, creatinine 1.97 mg/dL, uric acid 7.6 mg/dL, creatine kinase 1,497 IU/L, lactate dehydrogenase 973 IU/L, and myoglobin 2,150.8 ng/mL (Table 1). Serum concentration of cyclosporine was 66.3 ng/mL, which was within the therapeutic range. Her previous laboratory tests, performed 3 weeks earlier, showed normal serum transaminase levels and serum creatinine of 1.00 mg/dL. Serology for viral hepatitis was negative. A presumptive diagnosis of colchicine toxicity was made based on medication history and myoneuropathy with liver and kidney involvement. Colchicine and rosuvastatin were stopped immediately, and the patient was admitted. Levels of serum creatinine, creatine kinase, and lactate dehydrogenase began to fall on the day after admission. Epigastric discomfort and nausea began to improve on hospital Day 2. Serum transaminases also started to decline on the same day. Her tingling sensation and numbness had been on the slow improve and remained until discharge 8 days later. Two weeks after discharge, her paresthesia remained on both feet, but was improving gradually. The levels of serum transaminases, creatinine, and muscle enzymes returned to normal. Rosuvastatin was restarted, but her symptoms and laboratory abnormalities did not recur thereafter. Prednisolone 5 mg was prescribed to be used in an "as-needed" basis for acute exacerbation of gout. She had reported two acute attacks since October 2011, which responded well to prednisolone. Since then, she had no acute attack and her serum uric acid has remained at an optimal level.

Discussion

Previous case reports of colchicine myoneuropathy in patients with concomitant administration of cyclosporine were searched on MEDLINE, using the phrase "colchicine AND cyclosporine AND toxicity." Among 48 results, case reports were selected, whose demographic and clinical characteristics are summarized in Table 2.

In 10 out of 13 cases, patients were male, which is in accordance with the male-to-female incidence ratio of gout. Mean age of the affected patients was 56.9 ± 10.0 years. Doses of colchicine were 1 mg/d or lower in most of the cases, but doses higher than 1 mg/d were administered in three cases. Development of colchicine toxicity after its chronic use was reported in one case, after 8 years [7]. However, serum concentration of cyclosporine was also found to be at a toxic level in this case, so possibility of cyclosporine toxicity cannot be ruled out. Excluding this extreme, the mean duration of colchicine use was 12.6 ± 9.7 days. Side effects have been reported after 2 days or 3 days of colchicine administration [4,6,10]. Serum colchicine concentration was measured only in one case, which was within the therapeutic range. Serum concentrations of cyclosporine were above 400 ng/mL in three cases, and above 1,000 ng/mL in two of them. High serum cyclosporine level in these patients raises suspicion of cyclosporine toxicity, but it might be secondary to acute kidney injury due to colchicine toxicity. Signs of myopathy and hepatic involvement were universal in reported cases. Serum creatinine was above the normal range in all cases in which creatinine level was reported, but the degree of kidney injury was difficult to estimate due to a lack of data on baseline serum creatinine level. Neutrophil count was below the normal range in two cases, which was also seen in our patient. All patients recovered after cessation of colchicine. Laboratory abnormalities were usually normalized within 2 weeks, but complete recovery from weakness and paresthesia took longer than a month in most of the cases reviewed.

Colchicine binds to tubulin in a poorly reversible manner [12], preventing its polymerization, which is required for the formation of a microtubule. Microtubules are involved in cell division, signal transduction, regulation of gene expression, and migration of cell. Concomitant administration of cyclosporine increases the risk of colchicine toxicity. It is suggested that this might be due to strong inhibition of the membrane P glycoprotein by cyclosporine [8,13]. A drug–drug interaction

Table 1. Laboratory findings of the patient

Serum concentration	Day*									
	–20	0	1	2	3	4	5	6	7	22
CK (IU/L)		1,497	1,239	2,316		1,177	499			87
LD (IU/L)		973	761			711	629			492
AST (U/L)	23	166	168	227	176	124	67	54	44	23
ALT (U/L)	28	118	115	153	162	149	106	91	75	25
BUN (mg/dL)	30.8	26.4	23.8	16.7	12.5	14.6	18.7	14.7	14.3	16.1
Creatinine (mg/dL)	1	1.97	1.71	1.42	1.27	1.09	0.98	0.99	0.83	1
ANC (10*/μL)	4.67	4.569		1.7	1.71	1.58	1	1.64	2.41	5.25
Cyclosporine (ng/mL)	63.5	66.3								56.8

* Day –20 denotes the day colchicine was prescribed. On Day 0, the patient visited the emergency department and colchicine was discontinued. The patient was discharged on Day 8. On Day 22, the patient visited the outpatient clinic.
ALT, alanine transaminase; ANC, absolute neutrophil count; AST, aspartate transaminase; BUN, blood urea nitrogen; CK, creatine kinase; LD, lactate dehydrogenase.

Table 2. Clinical characteristics of 13 previous case reports

No	Refs	Sex	Age (y)	Transplanted organ(s)	Colchicine dose (mg/d)	Duration of colchicine use	Serum concentration (colchicine; ng/mL)	Cyclosporine dose (mg/d)	Serum concentration (cyclosporine; ng/mL)	Symptoms	CK (IU/L)	LD (IU/L)	Myoglobin (ng/mL)	BUN (ng/mL)	Cr (mg/dL)	AST (IU/L)	ALT (IU/L)	Neutrophil (cells/mm^3)
1	[6]	M	49	Kidney	2.4	3 d		250	267	Pain, weakness	14,958	1,102	≥300		2.7	561	403	
2	[4]	M	70	Kidney	1	16 d				Weakness	425							
3	[4]	M	55	Kidney	1	2 d				Pain	1,840							
4	[4]	F	49	Kidney	1	26 d				Pain	1,234							
5	[4]	M	56	Kidney	1	11 d				Pain	251							
6	[4]	M	67	Kidney	1	10 d				Pain, weakness	1,135							
7	[7]	M	53	Heart		8 y		350	1,450	Weakness, pain, fatigue	≥3,000			36	2.9			
8	[7]	M	56	Heart	0.6			450	≥2,000	Weakness, fatigue	449			43	1.9			
9	[7]	F	57	Heart	0.6			120		Weakness	700							
10	[9]	M	72	Kidney	1	30 d		150	134	Pain, weakness	766	1,102			1.2	170		
11	[3]		62	Kidney	2 for 3 d, 1 mg qod for 5 d, then 1 for 9 d	17 d		250		Constipation, nausea, abdominal pain, fatigue, confusion, arrhythmia	2,671	898			2.27	341	321	1,300
12	[10]	M	60	Heart	1	3 d	7	350	475	Fever, dyspnea, tachycardia, arrhythmia	1,553		2,188	23.1	7.9	2,061	3,074	700
13	[11]	M	34	Heart, lung	1 mg tid for 1 d, 1 mg bid for 1 d, then 1 for 6 d	8 d	13	340	111	Cough, dyspnea, diarrhea, general weakness	3,206		573	52.7	2.44	122	136	

ALT, alanine transaminase; AST, aspartate transaminase; bid, twice daily; BUN, blood urea nitrogen; CK, creatine kinase; Cr, creatinine; LD, lactate dehydrogenase; q.o.d, four times daily; tid, three times daily.

study performed *in vivo* revealed that cyclosporine increases total exposure, half-life, and peak concentration of colchicines significantly [14].

Regarding diagnosis, temporal relations and distinctive syndrome of muscle injury and symptoms suggesting peripheral neuropathy should raise suspicion of colchicine toxicity. No specific test provides a definitive diagnosis, but muscle biopsy and electromyography/nerve conduction studies were performed frequently in previous cases. The characteristic histological features of colchicine myopathy are vacuolar myopathy—the presence of lysosomes and autophagic vacuoles [2,6,9]. Absence of inflammatory finding is useful to exclude polymyositis.

Electromyography and nerve conduction studies may also demonstrate distinctive features. Myopathic motor unit potentials and early recruitment in proximal limb and truncal muscles, positive sharp waves, or complex repetitive discharges are seen. Reduced amplitude of motor and sensory responses, but normal or borderline-slow conduction velocities, which suggests mild axonal neuropathy, can be seen in nerve conduction studies [9].

It is questionable whether muscle biopsy or electrodiagnostic studies are always necessary for the diagnosis. They are often helpful in ruling out other diseases of polymyositis and Guillain–Barré syndrome, respectively. However, polymyositis usually takes an insidious course over several months, and antinuclear antibodies are detected in up to 80% of patients with dermatomyositis or polymyositis. Guillain–Barré syndrome does not cause prominent muscle injury as observed in cases of colchicine toxicity. Therefore, those invasive tests can be reserved for atypical presentation or delayed recovery after cessation of colchicine.

The mainstay of treatment is a prompt cessation of colchicine and supportive care. Colchicine is not removed by dialysis [15], and there is no proven treatment to reduce the serum concentration of colchicine. Thus, currently, the highly qualified intensive care with organ support is the only option in severe cases. Artificial liver or organ transplantation could be theoretically possible options, but have never been practiced in this condition.

Treatment of gout is complicated in those patients who have experienced colchicine toxicity. Corticosteroid and NSAIDs remain as alternative options for the management of acute exacerbation. A short course of oral corticosteroid is a safe and effective treatment option, especially considering nephrotoxicity of NSAIDs. Control of hyperuricemia and avoidance of risk behaviors cannot be overemphasized, as colchicine cannot be taken for the prevention of acute gout attack.

Colchicine can cause severe myoneuropathy with multiorgan involvement, and its risk is increased in patients with concomitant use of cyclosporine. Withdrawal of colchicine usually results in rapid clinical improvement, but associated mortality has also been reported. Thus, clinical suspicion and prompt cessation of colchicine are very important. In addition, invasive and costly diagnostic tests can be avoided by a timely diagnosis. Therefore, all physicians who are involved in the care of renal transplant recipients should be familiar with colchicine-induced myoneuropathy.

Conflict of interest

All authors declare no conflict of interest.

References

[1] Lin HY, Rocher LL, McQuillan MA, Schmaltz S, Palella TD, Fox IH: Cyclosporine-induced hyperuricemia and gout. *N Engl J Med* 321: 287–292, 1989

[2] Kuncl RW, Duncan G, Watson D, Alderson K, Rogawski MA, Peper M: Colchicine myopathy and neuropathy. *N Engl J Med* 316:1562–1568, 1987

[3] Minetti EE, Minetti L: Multiple organ failure in a kidney transplant patient receiving both colchicine and cyclosporine. *J Nephrol* 16: 421–425, 2003

[4] Ducloux D, Schuller V, Bresson-Vautrin C, Chalopin JM: Colchicine myopathy in renal transplant recipients on cyclosporin. *Nephrol Dial Transplant* 12:2389–2392, 1997

[5] Jagose JT, Bailey RR: Muscle weakness due to colchicine in a renal transplant recipient. *N Z Med J* 110:343, 1997

[6] Lee BI, Shin SJ, Yoon SN, Choi YJ, Yang CW, Bang BK: Acute myopathy induced by colchicine in a cyclosporine-treated renal transplant recipient–a case report and review of the literature. *J Korean Med Sci* 12:160–161, 1997

[7] Rana SS, Giuliani MJ, Oddis CV, Lacomis D: Acute onset of colchicine myoneuropathy in cardiac transplant recipients: case studies of three patients. *Clin Neurol Neurosurg* 99:266–270, 1997

[8] Gruberg L, Har-Zahav Y, Agranat O, Freimark D: Acute myopathy induced by colchicine in a cyclosporine treated heart transplant recipient: possible role of the multidrug resistance transporter. *Transplant Proc* 31:2157–2158, 1999

[9] Dupont P, Hunt I, Goldberg L: Warrens A: Colchicine myoneuropathy in a renal transplant patient. *Transpl Int* 15:374–376, 2002

[10] Eleftheriou G, Bacis G, Fiocchi R, Sebastiano R: Colchicine-induced toxicity in a heart transplant patient with chronic renal failure. *Clin Toxicol (Phila)* 46:827–830, 2008

[11] Bouquie R, Deslandes G, Renaud C, Dailly E, Haloun A, Jolliet P: Colchicine-induced rhabdomyolysis in a heart/lung transplant patient with concurrent use of cyclosporin, pravastatin, and azithromycin. *J Clin Rheumatol* 17:28–30, 2011

[12] Simkin PA, Gardner GC: Colchicine use in cyclosporine treated transplant recipients: how little is too much? *J Rheumatol* 27: 1334–1337, 2000

[13] Speeg KV, Maldonado AL, Liaci J, Muirhead D: Effect of cyclosporine on colchicine secretion by the kidney multidrug transporter studied *in vivo*. *J Pharmacol Exp Ther* 261:50–55, 1992

[14] Terkeltaub RA, Furst DE, DiGiacinto JL, Kook KA, Davis MW: Novel evidence-based colchicine dose-reduction algorithm to predict and prevent colchicine toxicity in the presence of cytochrome P450 3A4/P-glycoprotein inhibitors. *Arthritis Rheum* 63:2226–2237, 2011

[15] Wilbur K, Makowsky M: Colchicine myotoxicity: case reports and literature review. *Pharmacotherapy* 24:1784–1792, 2004