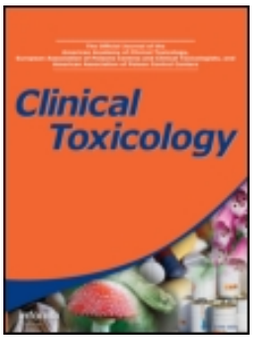

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CASE REPORT

Colchicine-induced toxicity in a heart transplant patient with chronic renal failure

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Introduction. Therapeutic doses of colchicine in patients with renal compromise and cyclosporine therapy may result in increased plasma concentrations of colchicine and colchicine toxicity. *Case Report.* A 60-year-old heart transplant patient with chronic renal failure and cyclosporine-induced immunosuppression was started on colchicine for suspected gout. Four days later, he developed multi-organ failure with rhabdomyolysis, liver damage, polyneuropathy, and cardiotoxicity. Colchicine intoxication was suspected and plasma levels were 7 ng/mL 36 hours after the sixth dose. Neutropenia with an absolute neutrophil count of 700 cells/mm^3 was observed five days after colchicine discontinuation. Drug discontinuation, supportive care, antibiotic therapy for a concurrent infection, and G-CSF administration resulted in recovery and he was discharged from the hospital 3 weeks later. *Discussion*. Cyclosporine co-administration increases colchicine toxicity by a dual mechanism: cyclosporine inhibits P-glycoprotein resulting in increased intracellular colchicine concentrations and decreased hepatic and renal excretion of the drug and cyclosporine interacts with CYP3A4 to decreases the hepatic elimination of colchicine. On the other hand, colchicine may increase cyclosporine neurotoxicity by an addictive mechanism. *Conclusions*. Short-term administration of therapeutic colchicine doses may cause life-threatening side effects in cyclosporine-treated patients with renal failure.

Keywords Intoxication; Chronic renal failure; Acute; Colchicine; Cyclosporin

Introduction

Colchicine is an effective treatment for acute gouty attacks in patients with normal kidney function, but impaired renal clearance may lead to accumulation and severe side effects. Colchicine toxicity usually presents with gastrointestinal symptoms, leukocytosis followed by severe pancytopenia, and multiorgan failure. These effects are mainly related to long-term use (1,2) or acute intoxication following an overdose (3,4). Moreover, short term administration of colchicine may be deleterious in some patients and adverse effects could be induced by the concomitant administration of cyclosporine, which suppresses P-glycoprotein (5,6). This report describes a case of life-threatening colchicine toxicity in a heart transplant patient with chronic renal failure and cyclosporine-induced immunosuppression.

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Case report

A 60-year-old man was transferred to our department because of cardiac arrhythmia, vomiting, diarrhea, profound asthenia and diffuse muscular pain. He underwent heart transplantation eight years before. Progressive renal failure, possibly due to calcineurin inhibitors, led to the initiation of dialysis one week before. He was treated with darbepoetin alfa, clonidine, amlodipine, clopidogrel, lansoprazole, furosemide, ramipril, methyldopa, sulfinpyrazone, and cyclosporine 175 mg/day. When hemodialysis was initiated, hypocalcemia (reference 8.7 to 10.3 mg/dL) and hyperphosphatemia (reference 2.25 to 4.75 mg/dL) were present. Results are shown in Table 1. Three days later, in order to relieve ankle pain possibly due to an acute gouty attack, his doctor prescribed colchicine 1 mg/day. Within three days, the patient developed vomiting, diarrhea, asthenia, myalgia, and a mild fever (37.6°C). At the beginning of symptoms he had already received 3 mg of colchicine but the drug was not discontinued for another three days resulting in a cumulative dose of 6 mg of colchicine. Over the following two days, the patient developed fever (39.9 °C), dyspnea, tachycardia (140 beats/minute), and supraventricular arrhythmias. Six days after the first dose of colchicine, oxygen saturation was 92% on 6 L/minute of oxygen. A transthoracic echocardiogram revealed a reduction of the ejection fraction from 45% to 25%. Sustained supraventricular tachycardia was

observed and was treated with amiodarone. The electrocardiogram showed ST segment depression in leads V2 and V3 and a pre-existing right bundle branch block associated left anterior hemiblock. A chest x-ray showed a mild right lower pulmonary lobe infiltrate; blood cultures were positive for methicillin-sensitive *Staphylococcus aureus* and vancomycin was begun at 1 g loading dose followed by 200 mg after each hemodialysis, three times a week for two weeks; subsequent blood cultures yielded negative results. The patient developed rhabdomyolysis and elevated liver enzymes. Time course of laboratory results are shown in Table 1. Cardiac troponin I concentration rose to 0.6 ng/ml (reference <0.2 ng/mL) on the sixth day after the first dose of colchicine. Liver and muscular enzymes peaked on the 8th day after the first dose of colchicine: alanine aminotransferase 2061 U/L (reference 3 to 46 U/L), aspartate aminotransferase 3074 U/L, (reference 3 to 46 U/L), creatine kinase 1553 U/L (reference 37 to 186 U/L) and serum myoglobin 2188 ng/ml (reference 18 to 61 ng/mL). Neutropenia (700 cells/mm^3) developed on the 11th day after the first dose of colchicine administration, five days after its discontinuation. Serologic tests for hepatitis A, B, C, were negative as well as all immunoserologic markers for autoimmune hepatitis; no evidence of malignancy was observed.

Cyclosporine blood concentration levels rose from 130 ng/mlL (reference 100 to 150 ng/mL) to 475 ng/ml and cyclosporine doses were reduced. Colchicine serum concentrations were 7 ng/mL 36 hours after the last colchicine administration (reference 1 to 4 ng/mL), 6.5 ng/mL at 50 hours and 5 ng/mL at 74 hours.

Within 2 to 3 days after colchicine discontinuation, symptoms improved although diffuse myalgia persisted. The ejection fraction rose to 40% and supraventricular arrhythmias disappeared within two days of colchicine discontinuation. On the day of severe neutropenia, a single subcutaneous dose of G-CSF (300 μg) was administered. Total WBC and absolute neutrophil counts increased. Thereafter, a progressive normalisation of laboratory results was observed, although dyspnea due to muscular weakness persisted for 15 days and severe asthenia disappeared within 20 days after colchicine discontinuation. The patient was discharged 27 days after colchicine discontinuation with no symptoms and normal laboratory values.

Discussion

Most organ transplant patients receive cyclosporine-based immunosuppression. Common side effects are hypertension, gingival hyperplasia, tremor, hirsutism, and mild-to-moderate hyperbilirubinemia. Acute and chronic nephrotoxicity may occur (7,8). Cyclosporine rarely may induce acute myopathy (9,10) and neurotoxicity (11,12).

Cyclosporine co-administration increases colchicine toxicity by a dual mechanism. First, cyclosporine inhibits P-glycoprotein resulting in increased intracellular colchicine concentrations and decreased hepatic and renal excretion of the drug (13). Second, cyclosporine interacts with CYP3A4 (14) to decreases the hepatic elimination of colchicine (15). On the other hand, colchicine may increase cyclosporine neurotoxicity by an addictive mechanism.

Colchicine intoxication has been reported with high dosages, especially in patients with renal failure. Common adverse reactions include nausea, vomiting, abdominal pain and diarrhea. A dose-related adverse effect of colchicine is

Table 1. Results of laboratory tests

	Days after first dose of colchicine administration					
Variable	4th–5th day	6–7th day	8th day	9th–10th day	11th day	12thday
Red cell-count (10^6 per mm^3)	3.57	3.92	3.22	2.93	2.87	3.09
White cell-count (10^3 per mm^3)	11.69	15.46	6.88	2.72	2.16	9.17
• Neutrophils (10^3 per mm^3)		14.58	6.25	1.68	0.7	5.9
• Lymphocytes (10^3 per mm^3)		0.6	0.41	0.25	0.48	0.88
Platelet count (10^3 per mm^3)	191	195	122	95	96	90
C-reactive protein (mg/dl)	5.6	14.2	16.7	8.1	6.9	6.2
Calcium (mg/dl)		8.2	6.7	7.8		7.6
Phosphatemia (mg/dl)		7.4				
Creatinine (mg/dl)		6	7	6	7.3	7.9
Urea nitrogen (mg/dl)		141	190	155	188	231
Aspartate aminotransferase(U/L)		775	3074	947	1271	116
Alanine aminotransferase(U/L)		376	2061	1679		684
Creatine kinase CK (U/L)	115	685	1553			
Myoglobin (ng/ml)		4067	5188	3649		
Troponin I (ng/ml)	0.17	0.6	0.31	0.13		0.06
Cyclosporine (ng/ml)		475		155	130	
Colchicine (ng/ml)			7	6.5	5	

myelosuppression, most notably neutropenia. Other manifestations of colchicine toxicity include renal failure, hepatic damage, polyneuropathy, myopathy, rhabdomyolysis and cardiovascular effects including heart failuar and ventricular arhythmias (16–18)colchicine have been reported to be 7 to 60 milligrams (19) and dosages of 0.5 to 0.8 mg/kg may be fatal (20,21). Because of the large apparent volume of distribution, rapid tissue distribution, and high affinity binding at intracellular sites, colchicine is not effectively removed by hemodialysis. Colchicine is partially deacetylated in the liver. Large amounts of colchicine and its metabolites re-enter the gastrointestinal tract via biliary and intestinal secretions and undergo enterohepatic circulation (22). The drug is excreted within 48 hours unchanged (14% to 40%) or as metabolites (4% to 14%) (23). An elimination half-life of 4.4 hours has been reported in patients with normal renal function and 18.8 hours in patients with renal failure (24); in a single study, the plasma half-life in elderly males was 30 hours (21).

Concurrent use of cyclosporine and colchicine may result in gastrointestinal dysfunction, hepatonephropathy, and neuromyopathy due to combined toxicity (25,26). Prompt discontinuation of colchicine and reduction in cyclosporine doses may improve the toxicity of this association.

Our patient was given colchicine for ankle pain presumably due to gouty attack. He subsequently developed pneumonia and positive blood cultures for Staphylococcus and septic arthritis was considered in the differential diagnosis of ankle pain.

Although concurrent bacteremia may heighten susceptibility to septic arthritis, this suspicion was judged unlikely since the concomitant localized swelling, effusion or tenderness of ankles were observed: the mild bilateral ankles pain subsided within three days.

In our patient, we observed toxicity that could be attributed to colchicine (cardiomyopathy, rhabdomyolysis, hepatocellular damage, peripheral neuropathy, severe neutropenia) or cyclosporine (hepatotoxicity, neuropathy) after the administration of 0.06 mg/kg of colchicine. Cyclosporine toxicity was probably not responsible for muscle damage since the whole blood cyclosporine levels were within the therapeutic range and the myopathy improved despite continuous administration of this drug.

Although uncommon, several cases of neutropenia have been reported following colchicine exposure, as an adverse reaction or drug intoxication. Most of these reports involve massive overdoses; long-term administration has also been associated with this adverse effect, but neutropenia has been rarely reported after usual therapeutic intake (4, 27). Our patient developed significant neutropenia and was treated with a single dose of G-CSF with dramatic WBC response.

Colchicine's cardiotoxicity includes bradycardia, sinus tachycardia, complete atrioventricular block, ventricular fibrillation and cardiac arrest and, occasionally, ventricular tachycardia (28). Our patient developed a severe reduction of ejection fraction, supraventricular arrhythmias and release of troponin I.

Myopathy and myoneuropathy have been described in association with regular use of colchicine and typically develop after several weeks of colchicine use (29–31). Colchicine could cause rhabdomyolysis by disrupting the microtubule-dependent cytoskeletal network that interacts with lysosomes (32,33). Acute myopathy following low-dose colchicine treatment during cyclosporine administration in transplant patients has been observed (34,35). The risk of myopathy is much greater in patients with renal compromise and in patients who receive concurrent cyclosporine administration.

Since our patient had a concomitant pneumonia, the constellation of symptoms that our patient presented may be attributed to sepsis. In this case it is important to determine which of the patient's subsequent problems were due to sepsis and which were sufficiently unlikely to be due to the infection that an alternative diagnosis is indicated.

Tachycardia and fever may be attributed to the infective disease and they subsided quickly with the beginning of antibiotic therapy but, in our opinion, sepsis might not account for all the features of our patient's illness.

This patient did not have septic shock since blood pressure never dropped under 110 mm Hg and, therefore, this diagnosis is inconsistent with the severe rhabdomyolysis and liver damage. Moreover, myocardial damage, neurotoxicity, neutropenia, vomiting and diarrhea were observed in the presence of colchicine blood levels in the toxic range and these abnormalities are the most common side effects reported in the literature on colchicine toxicity.

Conclusions

Colchicine toxicity was the most probable cause of the severe clinical picture displayed by our patient. Our case report suggests that therapeutic doses of colchicine in patients with renal compromise and cyclosporine therapy may result in high blood concentrations of colchicine and life-threatening colchicine toxicity. Close monitoring of these patients is essential.

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