
Colchicine neuromyopathy: A report of six cases

M.R. Altıparmak, Ö.N. Pamuk, G.E. Pamuk, V. Hamuryudan¹, R. Ataman, K. Serdengeçti

Department of Nephrology and ¹Department of Rheumatology, Cerrahpasa Medical School, University of Istanbul, Istanbul, Turkey.

Mehmet Rıza Altıparmak, MD, Resident-in-Chief; Ömer Nuri Pamuk, MD; Gülsüm Emel Pamuk, MD; Vedat Hamuryudan, MD, Professor of Medicine; Rezzan Ataman, MD, Professor of Medicine; Kamil Serdengeçti, MD, Professor of Medicine.

Please address correspondence and reprint requests to: Dr. Mehmet Rıza Altıparmak, Rasimpasa Mah. Tasli Bayir Sok. no. 14 Daire 10, Kadıköy-Istanbul, Turkey. E-mail: gepamuk@yahoo.com

Received on January 22, 2001; accepted in revised form on July 13, 2001.

Clin Exp Rheumatol 2002; 20 (Suppl. 26): S13-S16.

© Copyright CLINICAL AND EXPERIMENTAL RHEUMATOLOGY 2002.

Key words: Colchicine toxicity, neuropathy, myopathy, renal failure.

ABSTRACT

Colchicine has been in use for therapeutic purposes for many years. It can, however, cause subacute onset muscle and peripheral nerve toxicity in patients with chronic renal failure. In this report we describe 6 patients who developed neuromyopathy after the administration of colchicine. All patients presented with proximal muscle weakness, elevated serum creatine kinase (CK) levels, and neuropathy and/or myopathy on electromyography (EMG). The diagnosis of colchicine toxicity was confirmed in all cases by the normalization of CK levels and EMG after discontinuation of the drug. Toxicity developed in 4 renal failure patients on therapeutic doses of the drug, while one patient took a massive dose for suicidal reasons, and the other was on high-dose therapy. Patients using colchicine – especially those with renal failure – should be warned about the side effects of the drug and physicians should be careful in the administration of the drug.

Introduction

Colchicine is used in the treatment of various diseases such as gout, familial Mediterranean fever (FMF), and Behçet's disease (1-3). It causes derangement in the formation of microtubules, and arrests mitosis and other microtubule-dependant functions (4). The main side effects of colchicine are nausea, abdominal cramps and diarrhea, which are usually reversible (5,6). Serious toxic effects such as bone marrow suppression, disseminated intravascular coagulation, and cell injury in the kidney, liver and the central nervous system have generally been reported with very high doses of the drug or in patients with renal failure (7, 8). However, toxicity with standard doses has been also reported in patients with gout or FMF and renal failure (8). In myopa-

thy associated with colchicine, weakness of the proximal muscles, increased creatine kinase (CK) levels, and short or low motor-unit potentials on electromyography (EMG) are seen. In neuropathy related to colchicine, distal areflexia and mild sensory changes are detected. The first case of neuropathy and myopathy which developed in a woman using the drug chronically was described by Riggs *et al.* in 1986 (9). In recent years, some other cases reporting neuromyopathic side effects of the drug have been published (10, 11).

Although rarely reported, it is thought that colchicine myopathy may be more frequent in patients with renal failure who use colchicine at the usual doses (10). We report here our experience with 6 patients who developed neuromyopathy during treatment with colchicine.

Case reports

Case 1

A 48-year-old-male patient was referred to our hospital with weakness of the legs lasting for one month and epistaxis lasting for two days. The patient had a diagnosis of FMF and had been using colchicine for 11 years; his sister also had FMF. His attacks and complaints regressed with colchicine 0.5 mg 4 times a day; but the patient continued to use the drug only during attacks. He developed nephrotic syndrome and secondary amyloidosis 6 years ago and has been under regular hemodialysis for the last 3 years because of end-stage renal failure. He has been undergoing CAPD for the last 5 months.

Physical examination revealed weakness of all muscle groups in the lower extremities that was more prominent in the proximal region. Deep tendon reflexes (DTR) were normal bilaterally. There were no pathological reflexes or sensory loss. Laboratory values were as

follows: hemoglobin 9 gr/dl, WBC $3.1 \times 10^9/L$, platelets $61 \times 10^9/L$, ALT 1065 U/L (N: 5-42 U/L), AST 1107 U/L (N: 5-37 U/L), CK 1711 U/L (N: 25-190), LDH 1193 U/L (N: 160-480), urea 215 mg/dl (N: 10-40 mg/dL), creatinine 17.3 mg/dl (N: 0.5-1.4 mg/dL) and albumin 2.8 mg/dl (N: 3.5-5 mg/dL); calcium, phosphorus, uric acid and TSH levels were normal. Electromyographic (EMG) studies revealed brief, low motor-unit potentials of decreased amplitude in the proximal muscles. Muscle biopsy was not performed because of thrombocytopenia and the tendency to bleed. Colchicine was stopped given the toxicity. CPK, ALT, AST, LDH and the thrombocyte count became normal one month later, and the motor strength of the muscles was restored. Findings on EMG when repeated 6 months later were normal.

Case 2

A 32-year-old-male patient was admitted to our outpatient clinic with complaints of weakness and tiredness. He defined fever, abdominal pain, swelling and pain of the knees for 25 years. His brother and one sister were diagnosed as FMF; and, he was also prescribed colchicine at that time. The number of his attacks decreased with colchicine 0.5 mg/4 times a day. As his attacks became more frequent and his abdominal pain increased in the last 3-4 months, he increased colchicine to 0.5 mg/6-8 times a day. Physical examination revealed prominent weakness of all muscle groups. Laboratory values were: hemoglobin 13.9 gr/dl, WBC $7.4 \times 10^9/L$, platelets $232 \times 10^9/L$, ALT 22 U/L, AST 43 U/L, CK 3033 U/L, LDH 484 U/L, urea 28 mg/dl, creatinine 0.9 mg/dl, albumin 4.6 gr/dl; calcium, phosphorus, uric acid and TSH were normal. Electromyography demonstrated myogenic changes with spontaneous activity. Motor and sensory conduction velocities were mildly reduced. Colchicine was stopped and the patient's pain was controlled with NSAIDs. CK and LDH became normal in 1 month, he gained his previous muscle strength in 3 weeks. At his follow-up visit 3 months later, he was healthy and his EMG was normal.

Case 3

A 22-year-old-male was admitted to the outpatient clinics of our hospital complaining of weakness in the lower extremities and fatigue. He had a diagnosis of FMF since 9 years and amyloidosis was detected 3 years ago. He had irregular usage of colchicine 0.5 mg/4 times a day and he started to undergo hemodialysis 4 years ago. He has been performing CAPD for the last 2 years. Physical examination revealed weakness of all muscle groups in the lower extremities. Besides, there was minimal sensory loss on the tips of the fingers. The tendon reflexes were normal and equal bilaterally. Motor tonus and coordination were also normal, there were no pathological reflexes. Laboratory data were as follows: hemoglobin 15.5 gr/dl, WBC $8.1 \times 10^9/L$, platelets $55 \times 10^9/L$, ALT 45 U/L, AST 107 U/L, CK 2107 U/L, LDH 1154 U/L, urea 132 mg/dl, creatinine 9.9 mg/dl and albumin 1.63 gr/dl. He had 12 gr of proteinuria in 24 hours; other biochemical values were normal. EMG was performed which revealed very small sensory and motor action potentials of decreased amplitude and potential time in the proximal muscles. Having been diagnosed as colchicine toxicity, the patient was told to stop the drug. ALT, AST, LDH and CK levels became normal in 25 days. The motor and sensory functions turned to normal within 3 weeks, and the EMG was normal 2 months later.

Case 4

A 69-year-old-male patient who had progressive weakness in his lower extremities for nearly 2 months was referred to our hospital. He could not stand up from his chair and had difficulty in lifting objects up with his arms. He was using colchicine 0.5 mg/3 times a day for 15 years because of his gout. He was undergoing hemodialysis for 1 year as he had end-stage renal failure. Physical examination revealed weakness of the proximal muscles; and, the tendon reflexes were hypoactive in the arms and legs. In the distal parts of his feet, there were sensory disturbances and the vibration sense was decreased a little.

Laboratory studies were: hemoglobin 11.5 gr/dl, creatinine 9.4 mg/dl, CK 1072 U/L, LDH 484 U/L, AST 383 U/L, ALT 242 U/L. Findings compatible with axonal sensorimotor polyneuropathy were observed on EMG. These were evaluated as colchicine toxicity and the drug was stopped. Approximately 3 weeks later, the patient was able to stand up from his chair; and, motor strength of the proximal muscles and DTR were nearly normal. 6 weeks later, CPK, AST, LDH levels and EMG findings were totally normal.

Case 5

A 22-year-old female who swallowed 24 tablets of colchicine (0.5 mg each) was admitted to the emergency department with the complaints of nausea, vomiting, abdominal pain and diarrhea. She has been using colchicine 0.5 mg/4 times a day for 10 years as she was diagnosed as FMF. In physical examination, she was seen to have a tendency to sleep, blood pressure was 60/20 mm Hg, pulse rate was 114/minute and respiratory rate was 22/minute. Muscle strength could not be evaluated and DTR were hypoactive in all extremities.

Laboratory data were as follows: hemoglobin 12.4 gr/dl, WBC $10.3 \times 10^9/L$, platelets $242 \times 10^9/L$, urea 34 mg/dl, creatinine 2.4 mg/dl, uric acid 6.8 mg/dl, ALT 452 U/L, AST 384 U/L, CK 1452 U/L, LDH 618 U/L, all other biochemical values were within normal limits. As the patient had persisting hypotension despite therapy, she was transferred to the intensive care unit. Gastric lavage was performed and active charcoal was administered. On the third day of admission, her blood pressure became 100/65 mmHg. 3 weeks later CK levels turned to normal; and, the patient was discharged with normal clinical findings.

Case 6

A 41-year-old male patient presented with progressive muscle weakness and difficulty in climbing up stairs which developed in the recent 2 months. He was being followed as FMF for 15 years; and he had secondary amyloidosis and chronic renal failure for 4 years.

He was using colchicine for 11 years and the dosage of the drug was 0.5 mg/2 times a day for the last 4 years. In physical examination; he was found to have mild distal and proximal weakness in the lower extremities, and mildly decreased loss of sensation distally. Additionally, there were no DTR.

In laboratory studies, hemoglobin was 9.6 gr/dl, WBC $6.2 \times 10^9/L$, platelets $192 \times 10^9/L$, urea 86 mg/dl, creatinine 5.2 gr/dl, ALT 680 U/L, AST 524 U/L, LDH 812 U/L and CK 2420 U/L. Other biochemical values and TSH were normal. EMG showed spontaneous fibrillations and positive sharp waves in proximal and distal limb muscles. Sensory and motor nerve conduction studies demonstrated a mild axonal polyneuropathy. 10 days after stopping colchicine, CK, AST, ALT levels all became normal. 4 weeks later, the patient was able to nearly normal climb up the stairs with no problem and muscle strength was normal. The EMG performed 2 months later was also normal. start here

Discussion

Neuromyopathy related to drugs is not an infrequent complication. Colchicine causes painless, neuropathy-related vacuolar myopathy (12). In experimental studies, it was demonstrated that colchicine leads to a characteristic myopathy in animals (13). The mechanism of neuropathy caused by colchicine is not known accurately. There are studies which suggest that the pathogenesis of myopathy is the change in microtubular network produced by the drug (8). Colchicine affects both the skeletal muscles and peripheral nerves; however, the myopathy is more prominent, while axonal neuropathy is milder (8). The decrement in CK levels and the rapid improvement in EMG findings after discontinuance of the drug both support the hypothesis that the primary target of toxicity is the muscle.

Colchicine myopathy may be misdiagnosed as polymyositis initially (8). Polymyositis can have the same symptoms as colchicine toxicity, which are proximal weakness, increased CK levels, typical EMG and findings of myositis in muscle biopsy. Chronic uremic

myopathy is one of the conditions in which axonal neuropathy related to subacute myopathy is observed. Although distal symmetrical sensorimotor neuropathy is generally seen in uremia, proximal muscle weakness is also a frequent finding (14). In uremia, it is very rare to see increased CK levels. It is impossible for the signs of myopathy produced by both polymyositis and uremia to regress after discontinuing colchicine.

In our cases, the neuromuscular symptoms at initial presentation, increased CK levels and EMG findings are in favour of colchicine toxicity. However, the EMG findings were not very typical and muscle biopsy was performed in only one of the patients. The only available muscle biopsy was performed at a late stage and it did not disclose any specific finding. This might lead one to consider other etiologies apart from drug toxicity. On the other hand, the improvement in the clinical situation and the normalization of enzyme levels after stopping the drug support colchicine toxicity. A time period of 3-4 weeks elapsed after stopping the drug before CK and other signs of clinical myopathy regressed: this was compatible with previous observations (8). In the fifth case the symptoms became evident when high doses of the drug were ingested for suicidal purposes.

It is also known that colchicine might lead to bone marrow toxicity (5-7, 15). In our first case, pancytopenia was present on admission and this improved during follow-up after drug intake was stopped.

Plasma colchicine levels – no matter whether the drug is administered in its usual doses or not – might be elevated in subjects with liver and renal failure. In particular, patients with renal failure are at high risk of colchicine toxicity (16). In liver diseases plasma colchicine levels are high, but excretion of the drug is rapid. On the contrary, in patients with gout or renal failure plasma concentrations are similar; but the clearance rate of the drug is slower (16). There is knowledge that – in spite of giving the usual doses of colchicine – acute toxicity might be observed in patients with renal failure (17, 18). Seri-

ous renal failure, which was present in four of our cases, was probably the most important risk factor for the development of colchicine toxicity. Two of the patients used high doses of colchicine – one with therapeutic intention and the other for suicidal purposes.

Colchicine neuromyopathy is not a recently recognized entity. However, the drug is being used more and more often for the treatment of FMF and chronic renal insufficiency may develop as a late complication of amyloidosis in FMF. Our observations are interesting in that they draw attention to colchicine neuromyopathy in patients with FMF. Our experience suggests that patients – especially those with hepatic and renal failure – should be monitored for the toxicity of colchicine even when used in the conventional dose range of 1-2 mg/day, and that they should be advised to contact their physician in case of muscle pain and weakness, especially of the proximal muscle groups.

References

1. ZEMER D, PRAS M, SOHAR E, MODAN M, CABILI S, GAFNI J: Colchicine in the prevention and treatment of the amyloidosis of familial Mediterranean fever. *N Eng J Med* 1986; 314: 1001-5.
2. MIYACHI Y, TANIGUCHI S, OZAKI M, HORIO T: Colchicine in the treatment of the cutaneous manifestations of Behçet's disease. *Br J Dermatol* 1981; 104: 67-9.
3. GILMAN AG, GOODMAN LS, RALL TW, MURAD F (Eds.): *The Pharmacological Basis of Therapeutics*. 7th ed. New York, Macmillan 1985: 708-10.
4. LEVY M, SPINO M, READ SE: Colchicine: A state-of-the-art review. *Pharmacotherapy* 1991; 11: 196-211.
5. CARR A: Colchicine toxicity. *Arch Intern Med* 1965; 115: 29-33.
6. NAIDUS RM, RODVIEN R, MIELKE H: Colchicine toxicity: A multisystem disease. *Arch Intern Med* 1977; 137: 394-6.
7. BAUM J, MEYEROWITZ S: Colchicine: Its use as a suicidal drug by females. *J Rheumatol* 1980; 7: 124-7.
8. WALLACE SL, SINGER JZ, DUNCAN GJ, WIGLEY FM, KUNCL RW: Renal function predicts colchicine toxicity: Guidelines for the prophylactic use of colchicine in gout. *J Rheumatol* 1991; 18: 264-9.
9. RIGGS JE, SCHOCHET JR SS, GUTMANN L, CROSBY TW, DiBARTOLOME AG: Chronic human colchicine neuropathy and myopathy. *Arch Neurol* 1986; 43: 521-3.
10. KUNCL RW, DUNCAN G, WATSON D, ALDERSON K, ROGAWSKI MA, PEPER M: Colchicine myopathy and neuropathy. *N Eng J Med* 1987; 316: 1562-8.
11. DE DEYN PP, CEUTERICK C, SAXENA V,

- CROLS R, CHAPPEL R, MARTIN JJ: Chronic colchicine-induced myopathy and neuropathy. *Acta Neurol Belg* 1995; 95: 29-33.
12. LE QUINTREC JS, LE QUINTREC JL: Drug-induced myopathies. *Baillieres Clin Rheumatol* 1991; 5: 21-38.
13. SEIDEN D: Effects of colchicine on myofilament arrangement and the lysosomal system in skeletal muscle. *Z Zellforsch* 1973; 144: 467-73.
14. LAZARO PR, KIRSHNER HS: Proximal muscle weakness in uremia. *Arch Neurol* 1980; 37: 555-8.
15. WALLACE SL: Colchicine. *Semin Arthritis Rheum* 1974; 3: 369-81.
16. WALLACE SL, OMOKOKU B, ERTEL NH: Colchicine plasma levels. *Am J Med* 1970; 48: 443-8.
17. 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* 1997; 99: 266-70.
18. 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* 1997; 12: 160-1.