

Colchicine-induced neuromyopathy in a patient with chronic renal failure: the role of clarithromycin

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ABSTRACT

Neuromyopathy is a rare side effect of chronic colchicine therapy, most often occurring in patients with chronic renal failure. Drugs interacting with colchicine metabolism through CYP3A4 and P-glycoprotein can accelerate accumulation and toxicity. We describe a case of an interaction between clarithromycin and colchicine resulting in acute neuromyopathy, and we conclude that combined use of macrolides and colchicine should be avoided.

KEYWORDS

Clarithromycin, colchicine, CYP3A4, neuromyopathy, P-glycoprotein, simvastatin

INTRODUCTION

Neuromyopathy is a rare side effect of chronic colchicine therapy.^{1,2} We present a case of acute neuromyopathy in a patient with chronic renal failure who was taking colchicine for gouty arthritis. The side effect was probably induced by a drug interaction with clarithromycin prescribed for a pulmonary infection. The present case illustrates that use of colchicine for maintenance therapy, especially in patients with chronic renal failure, can lead to severe side effects. A temporary increase of the colchicine dose or the use of drugs that interfere with colchicine metabolism might turn out to be hazardous.

CASE REPORT

A 73-year-old man with chronic renal failure due to atherosclerosis and hypertension was admitted because of fatigue and myalgia in the upper and lower extremities. His medical history included severe cardiovascular disease (ischaemic heart disease with heart failure, and occlusion of the abdominal aorta), chronic obstructive airway disease, and gout. Because of an allopurinol-induced dermal vasculitis, he was switched to maintenance therapy with colchicine (0.5 mg once daily) one year before. Simvastatin therapy was instituted three months before admission (20 mg once daily).

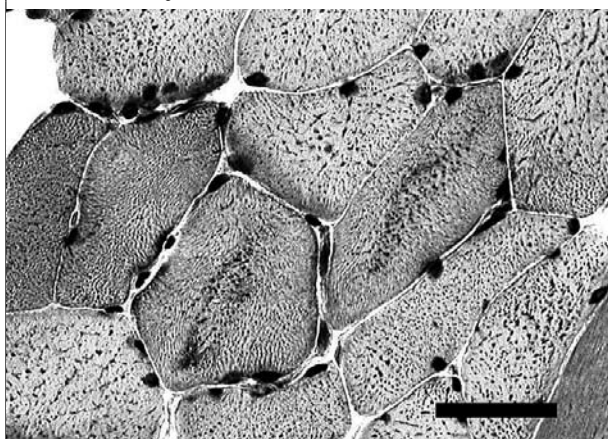
Two weeks before admission he was treated with clarithromycin for ten days because of pneumonia. One week later he developed fatigue, muscle weakness and muscle tenderness. Because of progression of these symptoms he was admitted to the hospital. He had neither fever nor any cardiac or respiratory symptoms. Cardiovascular, pulmonary and abdominal examination was unremarkable except for a pre-existent cardiac murmur. Neurological examination revealed general muscle weakness (Medical Research Council grade 4)3 and slightly decreased sensation of the lower extremities, with mainly his left foot affected. Minor symmetric hyporeflexia, but no myotonia was present.

On admission, laboratory examination revealed: haemoglobin 8.9 mmol/l, leucocyte count $3.2 \times 10^9/l$, thrombocyte count $78 \times 10^9/l$, creatinine 369 $\mu\text{mol/l}$, aspartate aminotransferase 219 U/l, alanine aminotransferase 345 U/l, creatine kinase (CK) 1396 U/l, lactate dehydrogenase 649 U/l, C-reactive protein <5 mg/l and erythrocyte sedimentation rate of 24 mm/hour. There were no signs of liver insufficiency. Serum electrolytes and thyroid-stimulating hormone were normal. Antinuclear antibodies and extractable

nuclear antigens were negative. Microbiological investigations showed no signs of viral infections or *Mycoplasma pneumoniae*. Radiological examinations were unremarkable.

It was suspected that the patient was suffering from a drug-induced neuromyopathy, and colchicine and simvastatin were discontinued. Electromyography (EMG) revealed polyphasic motor unit potentials with low amplitude and short duration, indicative of myopathy. No signs of myotonia or fibrillations were noticed. Furthermore, a sensory motor axonal polyneuropathy, mainly of the distal lower extremities, was seen. A muscle biopsy showed a vacuolar myopathy with multiple small vacuoles in the centre of the muscle fibre (*figure 1*). The lysosomal nature of these vacuoles was confirmed by a strong acid phosphatase positivity. In electron microscopy these lysosomes were filled with autophagic material. These observations were consistent with previously reported pathological features of colchicine toxicity. No signs of statin-induced myopathy, such as myonecrosis, were seen. After the discontinuation of colchicine a rapid decrease of the CK level and a rapid recovery of the pancytopenia occurred. The muscle weakness disappeared gradually in two weeks.

Figure 1. Muscle biopsy: characteristic multiple small basophilic vacuoles accumulated in the central part of several muscle fibers



The black bar represents 50 μ m. (Hematoxylin-Phloxine stained frozen section).

DISCUSSION

Our patient developed colchicine-induced neuromyopathy after low-dose colchicine therapy for more than one year. Since he had no liver failure, this probably resulted from chronic colchicine accumulation in the presence of his renal failure. However, the recent use of clarithromycin and

initiation of lipid-lowering therapy with simvastatin raise the possibility of a drug interaction, especially because both drugs share metabolic pathways with colchicine, namely via the CYP3A4 and the P-glycoprotein. Inhibition of these proteins increases serum colchicine levels, with accelerated accumulation and possible toxicity.

An interaction between simvastatin and colchicine appears less likely, because although both drugs are substrates of CYP3A4 and the P-glycoprotein, they have no relevant inhibitory effect on these metabolic pathways themselves.⁴ However, macrolides, including clarithromycin, are known inhibitors of the CYP3A4 and P-glycoprotein systems⁵ and have been shown to increase the colchicine serum level.⁶ Therefore, it is very likely that this inhibition by clarithromycin was responsible for the occurrence of colchicine-induced neuromyopathy in our patient. In support of this possibility are several recent reports on an interaction between clarithromycin and colchicine.^{7,8} In addition, in one retrospective study an incidence of severe toxicity in as much as 10% of patients receiving concomitant therapy with colchicine and clarithromycin is mentioned.⁹ However, these studies did not specifically regard the occurrence of neuromyopathy.⁷⁻⁹

Colchicine-induced neuromyopathy

Neuromyopathy due to colchicine therapy is infrequently encountered, and most often seen after chronic use in patients with renal or liver failure.^{10,11} Patients present with proximal muscle weakness and sometimes muscle tenderness. On neurological examination minor distal sensory loss and hyporeflexia can be found. Various degrees of serum level elevations of CK have been described, usually up to 10 times the upper limit of normal, but severe rhabdomyolysis can occur. Additional investigations are necessary to exclude myopathy caused by thyroid disease, viral infections and other drugs. EMG shows aspecific changes indicative for myopathy, with polyphasic motor unit potentials with low amplitude and short duration, and often a mild sensory motor polyneuropathy of the axonal type. On the contrary, muscle biopsy yields highly specific and pathognomic abnormalities, revealing a vacuolar myopathy with accumulation of autophagic vacuoles (*figure 1*).¹² Although muscle biopsy is not always necessary, in case of rapid recovery after cessation of colchicine, it may be necessary in cases where several drugs are the possible cause of myopathy and stopping either drug is not desirable.

The pathophysiological mechanism of colchicine-induced neuromyopathy has been studied in animal models.¹² Disruption of intracellular microtubule formation due to the toxic effects on tubulin results in disrupted exocytosis of autolysosomes with subsequent accumulation and formation of autophagic vacuoles, the last causing the typical image seen on muscle biopsy.

Colchicine toxicity results from elevated plasma levels due to altered pharmacokinetics. In otherwise healthy patients the elimination half time of colchicine is approximately 3 to 10 hours. The drug is partially demethylated in the liver by the cytochrome P450 system, mainly by the isoenzyme CYP3A4, and excreted as a metabolite or unchanged in the bile and urine by the P-glycoprotein.¹³ Colchicine undergoes enterohepatic recirculation.

In the presence of hepatic or renal failure accumulation occurs and toxicity is promoted at normal therapeutic doses. This can result in diarrhoea, neuromyopathy, elevated liver enzymes and pancytopenia often occurring simultaneously. Toxicity can be induced or accelerated by drugs interacting with colchicine metabolism such as macrolides, cyclosporin A, azoles and protease inhibitors.^{2,9} Cessation of colchicine and possible interacting drugs often results in quick recovery, although fatalities are not uncommon in case of severe pancytopenia.⁹ Therapy is supportive as there are no specific antidotes or methods to decrease toxic plasma levels.

CONCLUSION

We describe a case of acute colchicine-induced neuromyopathy in a patient with chronic renal failure who was on colchicine maintenance therapy. The toxicity was most probably accelerated by the addition of the CYP3A4 and P-glycoprotein inhibitor clarithromycin increasing colchicine serum levels. Although this interaction is increasingly recognised, our case was the first one reported to the Netherlands Pharmacovigilance Centre Lareb (safety report 45076). Care should be taken when prescribing colchicine as maintenance therapy, especially in patients with chronic renal failure who are taking many different drugs. Awareness of the pharmacokinetic properties of these drugs and their possible interactions remains crucial if toxicity is to be prevented. The combined prescription of clarithromycin or other CYP3A4 inhibitors and colchicine should be avoided.

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REFERENCES

1. Caglar K, Odabasi Z, Safali M, Yenicesu M, Vural A. Colchicine-induced myopathy with myotonia in a patient with chronic renal failure. *Clin Neurol Neurosurg* 2003;105:274-6.
2. Dupont P, Hunt I, Goldberg L, Warrens A. Colchicine myoneuropathy in a renal transplant patient. *Transpl Int* 2002;15:374-6.
3. Medical Research Council. Aids to the investigation of the peripheral nervous system. London: Her Majesty's Stationary Office 1975;1-2.
4. Prueksaritanont T, Vega JM, Rogers JD, et al. Simvastatin does not affect CYP3A activity, quantified by the erythromycin breath test and oral midazolam pharmacokinetics, in healthy male subjects. *J Clin Pharmacol* 2000;40:1274-9.
5. Yasuda K, Lan LB, Sanglard D, Furuya K, Schuetz JD, Schuetz EG. Interaction of cytochrome P450 3A inhibitors with P-glycoprotein. *J Pharmacol Exp Ther* 2002;303:323-32.
6. Tateishi T, Soucek P, Caraco Y, Guengerich FP, Wood AJ. Colchicine biotransformation by human liver microsomes. Identification of CYP3A4 as the major isoform responsible for colchicine demethylation. *Biochem Pharmacol* 1997;53:111-6.
7. Akdag I, Ersoy A, Kahvecioglu S, Gullulu M, Dilek K. Acute colchicine intoxication during clarithromycin administration in patients with chronic renal failure. *J Nephrol* 2006;19:515-7.
8. Rollet F, Pajot O, Chauvelot-Moachon L, Nazal EM, Kelaidi C, Blanche P. Acute colchicine intoxication during clarithromycin administration. *Ann Pharmacother* 2004;38:2074-7.
9. Hung IF, Wu AK, Cheng VC, et al. Fatal interaction between clarithromycin and colchicine in patients with renal insufficiency: a retrospective study. *Clin Infect Dis* 2005;41:291-300.
10. Wallace SL, Singer JZ, Duncan GJ, Wigley FM, Kuncel RW. Renal function predicts colchicine toxicity: guidelines for the prophylactic use of colchicine in gout. *J Rheumatol* 1991;18:264-9.
11. Wilbur K, Makowsky M. Colchicine myotoxicity: case reports and literature review. *Pharmacotherapy* 2004;24:1784-92.
12. Kuncel RW, Bilak MM, Craig SW, Adams R. Exocytotic "constipation" is a mechanism of tubulin/lysosomal interaction in colchicine myopathy. *Exp Cell Res* 2003;285:196-207.
13. Chappey O, Scherrmann JM. Colchicine: recent data on pharmacokinetics and clinical pharmacology. *Rev Med Intern* 1995;16:782-9.