Colchicine-induced myopathy and neuropathy

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Myopathy and neuropathy that have been induced by colchicine have been described only occasionally, although colchicine is a widely used drug. We describe a case of colchicine-induced myopathy and neuropathy in an 84-year-old woman who had renal impairment. Results from a muscle biopsy showed characteristic vacuolar myopathy and autophagic vacuoles. The cessation of medication resulted in a marked improvement of myopathy.

HKMJ 1999;5:204-7

Key words : Colchicine/adverse effects; Muscular diseases/chemically induced; Nervous system diseases/chemically induced

Introduction

Colchicine is derived from the corms of *Colchicum autumnale* and has been artificially synthesised for the treatment of gout. Although the drug has been used therapeutically for more than 200 years, myopathy that is associated with its long-term use in humans has not been reported frequently in the literature. This adverse reaction has only since 1996 been reported in the British National Formulary. We report on a case of colchicine-induced neuropathy and myopathy to illustrate the potential complications of long-term colchicine use.

Case report

An 84-year-old Chinese woman presented to the Department of Geriatrics at the Caritas Medical Centre on 12 July 1996 with a 2-week history of progressive weakness in the muscles of her arms and legs. The patient had found rising from chairs and lifting of objects difficult. She could no longer walk without support and had a feeling of slight numbness in her hands and toes. She had also been producing watery diarrhoea 2 weeks prior to hospital admission. In addition to having taken diltiazem, isosorbide mononitrate, aspirin, frusemide, and potassium chloride (which were given as out-patient medications to treat hypertension, ischaemic heart disease, and congestive heart failure) the patient had intermittently bought colchicine, cimetidine, and naproxen without prescription during the previous few years to treat gouty arthritis. Four weeks before admission to hospital, she had attended the geriatric clinic because of knee and ankle pain, and a course of colchicine 0.5 mg twice daily was started. No neurological signs or symptoms were noted at that time.

On admission to the Caritas Medical Centre, neurological examination showed marked proximal weakness and atrophy, which were distributed symmetrically but more in the legs than in the upper limbs. The scores on the Medical Research Council (MRC) scale were as follows: 2/5 for hip flexion; 3/5 for knee extension and flexion; 5/5 for feet dorsiflexion and plantarflexion; and 4/5 for shoulder abduction. The sensation of light touch decreased from the feet to knees, and slightly decreased on the hands. Deep tendon reflexes were absent in the legs and were weakly positive in the arms.

Routine blood tests gave normal results except for increased levels of serum creatine kinase 2559 U/L (normal range, 0-130 U/L), aspartate aminotransferase 176 U/L (normal range, 0-35 U/L) and lactate dehydrogenase 335 U/L (normal range, 50-150 U/L); a decreased white blood cell count of $3.3x10^9$ /L; moderately raised levels of serum creatinine 178 μmol/L (normal range, 50-110 μmol/L) and uric acid 561 μmol/L (normal range, 120-420 μmol/L); and a raised erythrocyte sedimentation rate of 82 mm/hr. Electrocardiography showed a strain pattern that indicated left ventricular hypertrophy.

Nerve conduction studies were performed on the right limb and showed a reduced amplitude of peroneal

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and tibialis anterior nerve responses and borderline/slow conduction velocities, which indicated axonal polyneuropathy. The sural nerve sensory potential was absent, and needle electromyography of the right tibialis anterior, rectus femoris, and biceps brachii showed spontaneous complex repetitive discharges in these muscles. The interference patterns in the electromyogram of the right tibialis anterior were suggestive of myopathic change and a reduced amplitude in the motor unit potential. The results from the biceps brachii interference pattern study were within normal limits but had borderline myopathic features. An interference pattern study of the rectus femoris was not successful, as the patient was too weak to give a sustained contraction of that muscle. A muscle biopsy of the quadriceps and a sural nerve biopsy were performed. Histological examination of the muscle fibres showed only non-specific features of slight variation in fibre size and a faint basophilic tinge at the subsarcolemmal region. Electron microscopy showed subsarcolemmal vacuoles of varying sizes that contained electron-dense lysosomal granules and autophagic material (Fig); these observations were consistent with previously reported features of colchicine induced myopathy.[1-3] The sural nerve biopsy sample was inadvertently fixed in formalin and hence was unsuitable for further study.

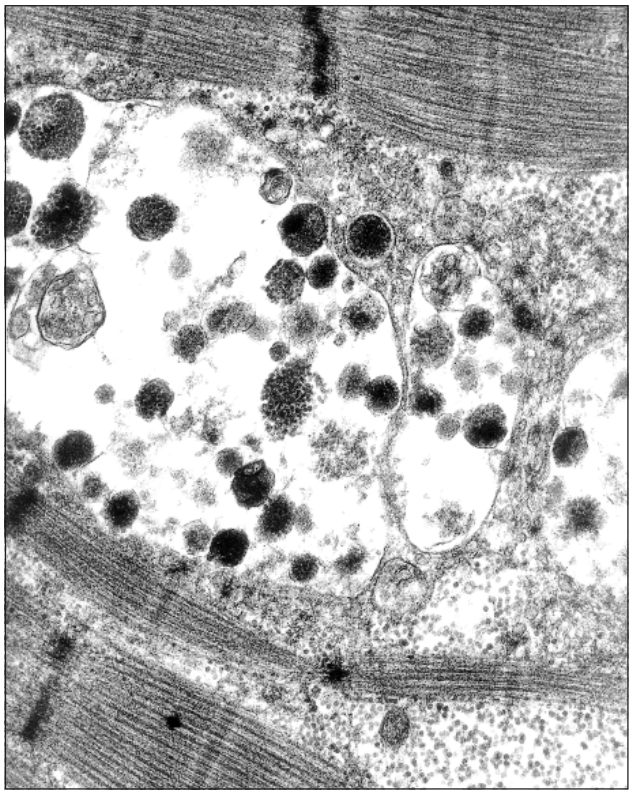

Fig. Electron micrograph of muscle showing cytoplasmic vacuoles containing heterogenous granular and membranous bodies, glycogen, and lysosomes (x11 820)

The results of the muscle biopsy were regarded as being consistent with colchicine-induced myopathy. Colchicine treatment was terminated and regular physiotherapy was commenced. The diarrhoea disappeared and the creatine kinase level gradually returned to normal. Muscle power gradually improved and 3 weeks later, hip flexion reached a score of 4/5 on the MRC scale and the patient was able to walk independently. The white blood cell count returned to normal (at 6.4×10^9 /L) in 2 weeks. Two and a half months later, electromyography of the right tibialis anterior showed an increased amplitude in the motor unit potential, which was suggestive of recovery from the colchicine induced injury. Complex repetitive discharge was no longer seen in the electromyographs. Meanwhile, the clinical and electrophysiological signs of the underlying mild distal neuropathy remained the same in the lower limbs, but there was some improvement in the amplitude of the evoked muscle action potential of the peroneal nerve. The sural nerve sensory potential remained absent bilaterally. The upper limb reflexes became stronger.

Discussion

Acute toxic side effects (other than gastro-intestinal upset) from the use of colchicine in the treatment of acute gouty arthritis are rare; any nausea or diarrhoea is usually reversible. Severe toxic effects such as bone marrow failure, acute neuritis, and ascending paralysis have been reported to occur among patients who had a prior hepatic or renal disease, or who had overdosed on colchicine.[4]

There are many drugs (including chloroquine, amiodarone, and vincristine) as well as conditions such as alcohol abuse, paraneoplastic syndrome, hypothyroidism, connective tissue disorder, and uraemia that cause combined myopathy and peripheral neuropathy; however, colchicine use is one of the less recognised causes. Because of the availability of colchicine over the counter, myoneuropathy may be a more common condition than expected. Kuncl et al[1] were the first to report on patients with colchicine-induced myopathy and neuropathy in 1987, and cases have been rarely reported since then.[1-3,5,6] In most cases, such as this case report, patients take customary levels of colchicine but toxicity develops due to varying degrees of renal impairment.[1,5,6] Neurological examination shows predominantly proximal muscle weakness, which is accompanied by distal areflexia and minor distal sensory loss. Electromyography shows myopathic changes, while electron microscopy of muscle biopsy samples shows vacuolar changes and an

accumulation of lysosomes and autophagic vacuoles.[1-3] Myopathy generally disappears a few weeks after the cessation of medication, but neuropathy may persist for a long time.[1,2]

The risk of combined myopathy and peripheral neuropathy is predominantly related to the presence of chronic renal insufficiency, which is indicated by an elevated serum creatinine level of >140 μmol/L.[1,4] Colchicine is readily absorbed and a peak serum level is reached 30 to 120 minutes after oral ingestion; the serum half-life is approximately 20 minutes. Colchicine becomes distributed into tissue space of a volume larger than that of body water within half an hour of administration.[7] When given orally or intravenously, colchicine undergoes enterohepatic circulation and accumulates in the liver, bone marrow, leukocytes, kidneys, intestines, spleen, and testes. The drug is partially monodemethylated in the liver by the cytochrome P450 system and excreted unchanged or as a metabolite in the urine and faeces. In normal human beings, 15% to 40% of the colchicine is excreted unchanged and 4% to 15% is excreted as metabolites within 48 hours. Thus, plasma colchicine levels will be elevated if there is hepatic or renal dysfunction, despite administration of ordinary oral doses.

Classically, neurotoxins or neurotoxic drugs induce axonal-type neuronal damage. Colchicine, however, inhibits the formation of microtubules, which are widely distributed tubular structures that are present in, for example, nerve cells, ciliated cells, leukocytes, and sperm tails. Microtubules are involved in cell motility and also form an intracellular transport network along which materials move by saltatory movements within cells. Tubulin, the subunit of microtubules, is a complex composed of two different polypeptide chains, and microtubules are usually in a stage of dynamic equilibrium with tubulin, which exists in a soluble pool. Colchicine binds to tubulin reversibly at a high-affinity site and prevents the polymerisation of tubulin into microtubules, thereby impairing axoplasmic transport in peripheral nerves.[8] Colchicine also alters the microtubular network that localises, moves, or allows the normal extrusion of lysosomes and autophagosomes in skeletal muscle cells.[1] The mechanism of colchicine myopathy may be due to the overdevelopment of autophagic vacuoles, which subsequently injure the lysosomal membrane, thereby increasing its permeability. Proteolytic enzymes may be released from these secondary lysosomes into the cytoplasm and may cause myofibril degenerative changes similar to chloroquine-induced vacuole myopathy.[9] This postulated mechanism merits further study.

Colchicine is a potentially toxic drug that has a narrow therapeutic window; its side effects outweigh the therapeutic benefit in chronic treatment. In the presence of neurological symptoms such as limb numbness or weakness, a possible diagnosis of colchicine-induced myopathy and neuropathy should be considered, especially in high-risk patients whose creatinine clearance is less than 0.83 mL/s (normal range, 1.24-2.08 mL/s).[10] The diagnosis should also be considered for patients who have coexistent hepatic dysfunction, or when there is co-administration of drugs that are capable of inhibiting liver enzyme activity—for example, calcium-channel blockers (eg diltiazem) and H_2-receptor antagonists (eg cimetidine).[11] In this patient, the rapid onset following 2 weeks of colchicine myopathy was due to the combination of renal impairment and the co-administration of diltiazem and cimetidine.[11] The co-administration of cimetidine has been reported to decrease colchicine clearance by 32% and to increase the half-life of colchicine by 33%.[12]

The hepatic metabolism of many drugs decreases with age, as some cytochrome P450–dependent mixed function oxidase activities become reduced. Colchicine should thus be used with caution in elderly patients and for daily prophylactic use; the dosage should begin at the lowest end of the usual range—for example, 0.5 mg/d. Colchicine in doses of 0.5 mg once daily has rarely induced myotoxicity even in patients with abnormal renal function.[10] The tenet "start low, go slow" should apply to the use of these agents in elderly patients to avoid unnecessary complications.

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