Case report

COLCHICINE MYOTOXICITY: A CASE REPORT

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Abstract
An 82 year-old woman with gouty arthritis developed acute diarrhea, vomiting, myalgia and generalized muscle weakness after she had mistakenly increased the dose of colchicine (0.6 mg/tablet) from once a day to three times/day for 1 week. She was found to have pancytopenia, proximal muscle weakness and elevated serum muscle enzymes. A clinical diagnosis of colchicine myotoxicity and hematotoxicity was made. Despite aggressive therapy, she died on the 5th hospital day. This patient represented another case of the rare side effect of colchicine, and the risk factors involved in the occurrence of colchicine toxicity is reviewed. Chiang Mai Med Bull 2004;43(2):87-92.

Keywords: colchicine, side effects, myotoxicity, rhabdomyolysis, pancytopenia

Colchicine is an alkaloid derived from the plant, Colchicum antumnale. It has been used to treat gout since the sixteenth century. Besides gout, it has also been used in a variety of illnesses including pseudogout, familial Mediterranean fever, primary biliary cirrhosis, scleroderma, sarcoidosis, amyloidosis, Behcet’s disease, and hepatic cirrhosis. Gastrointestinal side effects are the most recognized, and include abdominal pain, nausea, vomiting and diarrhea. These side effects pre-warn the patient and physician to discontinue the therapy, and prevent more serious consequences.

Major colchicine toxicities have included fever, rash, alopecia, bone marrow suppression, hepatotoxicity, pancreatitis, hypotension, arrhythmia, myocarditis, electrolyte imbalance, rhabdomyolysis, peripheral neuropathy, seizure, and coma. These toxicities are usually seen in those with renal and/or liver impairment.

The clinical feature of colchicine toxicity, after receiving a large amount of colchicine, can be divided into 3 stages. The first stage occurs within 24 hr after ingestion, with predominant gastrointestinal symptoms. The second stage is multi-organ failure including bone.

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morrow suppression and myoneuropathy, which usually occurs 24-72 hr later. The third stage is the recovery phase, with the resolution of organ dysfunction and development of alopecia, which occurs 7-10 days after the ingestion.

Myotoxicity and bone marrow suppression are well recognized symptoms of colchicine toxicity. The actual incidence of this condition is not known. Many sporadic cases have been reported in the English literature. However, this condition has rarely been described in Thailand. Only 3 cases have been reported in the Thai literature. We reported here another case of colchicine myotoxicity and pancytopenia in a patient suffering from gout, and emphasized its use in patients with renal impairment.

Case report

An 82-year-old woman who had gout for 2 years was prescribed colchicine (0.6 mg) and allopurinol (100 mg) once a day at a local hospital, but she mistakenly took her medication 3 times daily for 1 week. Four days later, she began to have diarrhea, nausea and vomiting and generalized myalgia without fever, and was admitted to her local hospital. Intravenous fluid and antibiotics were given with the presumptive diagnosis of acute gastroenteritis. On the fourth hospital day, she suffered progressive malaise and weakness, and was referred to our hospital. No details of past medical history or recent blood chemistry, particularly renal function, were available.

Her vital signs were as follows: blood pressure 120/90 mmHg, pulse rate 100/min, respiratory rate 20/min, and temperature 38.3 °C. She was mildly dehydrated, but with normal consciousness. Examination of the skin, heart and lungs were unremarkable. The abdomen was soft, with active bowel sounds. There was no area of localized tenderness, guarding or rigidity. Generalized muscle ache and pain was noted. Proximal muscle weakness with motor power was grade 2 and 5 in the proximal muscle and distal muscle groups, respectively. Sensation was intact. The deep tendon reflexes were decreased throughout. Cranial nerves were intact. No fasciculation was observed. There was no neck stiffness.

Initial complete blood count (CBC) showed hematocrit at 33.4 vol%, a white blood cell (WBC) count of 1,600 cells/mm³ with 91% neutrophils and 9% lymphocytes, and a platelet count of 167,000 cells/mm³. Urine examination revealed numerous WBCs, with many gram negative bacilli on Gram stained smears. Blood in the urine was positive without red blood cells. Blood chemistry showed blood urea nitrogen of 78 mg/dL (normal 7-24), serum creatinine of 3.9 mg/dL (normal 0.0-1.6), calcium of 6.7 mg/dL (normal 7.0-11.0), and phosphorus of 6 mg/dL (normal 2.5-4.5). Serum muscle enzymes showed creatine phosphokinase (CPK) of 10,450 U/L (normal 0-195), aspartate aminotransferase of 1,888 IU/L (normal 3-37), and lactate dehydrogenase of 2,258 U/L (normal 113-246). The MB CPK was normal. Serum and urine myoglobin were not performed. Thyroid function tests were consistent
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with euthyroid sick syndrome. A chest radiograph was unremarkable. An abdominal plain film showed increased bone density at the spine consistent with renal osteodystrophy. Ultrasound of the kidney showed bilateral hydronephrosis and hydrouraeter, but the obstruction sites were not demonstrated. Cerebrospinal fluid examination was normal.

The diagnosis of rhabdomyolysis, acute renal failure on-top of chronic renal failure, and urinary tract infection was made. Colchicine was discontinued. Intravenous ceftriaxone at 2 gm/day was given to cover the urinary tract infection. A granulocyte colony stimulating unit at 300 gm/day was given for neutropenia. Two days later, the patient had low grade temperature. A repeat CBC showed pancytopenia (hematocrite at 30.7 vol%, WBC count of 785/mm³, and platelet count of 43,000/mm³). Blood and urine culture showed no growth. Serum creatinine was 3.7 mg/dL. On the fourth hospital day, the patient’s condition declined. She developed high grade fever, delirium, hypotension with shock. Despite aggressive supportive therapy, she died on the fifth hospital day. Post mortem muscle biopsy performed 6 hours after the death showed muscle cell lysis. No myonecrosis was noted.

Discussion

This patient presented with acute gastroenteritis, followed by myopathy and pancytopenia shortly after she mistakenly increased her colchicine and allopurinol dosage for gout. Colchicine was believed to be responsible for this illness, based on the patient’s history and clinical syndrome. The discovery of urinary blood without the presence of red blood cells performed by a urine dipstick, and the absence of anemia at the time of admission, supported the presence of myoglobin in her urine. Unfortunately, the serum and urine myoglobin were not performed, as they are routinely unavailable at our institution. Furthermore, the patient did not take any drugs or have a history that suggested viral infection, which might explain the increase in serum muscle enzymes. Taking these findings together with the presence of generalized muscle ache and pain, muscle weakness, and elevation of serum muscle enzymes, rhabdomyolysis due to colchicine is the most likely diagnosis.

Colchicine myotoxicity has been well recognized and presents with subacute proximal weakness, muscle ache and pain, and elevation of the serum muscle enzymes in most patients. Serum CPK is a sensitive measure of colchicine myopathy, as the enzyme activity parallels the severity of the disease, and returns to normal with the recovery of proximal muscle strength. A CPK level 44 times above normal has been described. The majority of patients aged between 50-70 years who develop colchicine myotoxicity, receive oral colchicine at 1.2 mg/day or more. They also have renal insufficiency (mostly creatinine > 1.6 mg/dL), or creatinine clearances of 50 ml/min or less. Colchicine myotoxicity has rarely been described in patients with renal insufficiency who
take colchicine at 0.6 mg/day or less. The duration of colchicine ingestion does not seem to be related to the development of myotoxicity. Although our patient did not have a base line serum creatinine, the presence of renal osteodystrophy on the plain KUB supported the presence of chronic renal failure, rendering the patient at risk for the development of colchicine toxicity.

The muscle pathology in colchicine myopathy includes lysosomal and vacuolar changes without prominent necrosis. These pathological changes imply a microtubule-dependent cytoskeletal network interacting with lysosome, which is the result of the anti-microtubule property of colchicine. This distinctive pathology is useful in differentiating colchicine myopathy from other inflammatory myopathies. Muscle necropsy of our patient showed muscle cell lysis without muscle necrosis. The lysosomal and vacuolar changes were not observed. This might be due to the necropsy being performed 6 hours after death.

In spite of its well known anti-mitotic action, the hematologic side effects of colchicine are rare when used at a therapeutic dosage. Most reported cases in humans usually occur when taking a large amount of colchicine orally or intravenously. In animal models, subcutaneous injection of a large amount of colchicine into rabbits (5 mg/kg) and dogs (0.4 mg/kg) produced a rapid and transient reduction in circulating neutrophils and lymphocytes. By the time maximum depression of circulating leukocytes occurred, the cellularity of bone marrow remained unchanged. This finding suggests that administration of a large amount of colchicine causes rapid destruction of circulating leukocytes. The granulocytopenia can be rapidly restored by the use of granulocyte colony stimulating factor. Our patient, with impaired renal function, took oral colchicine at 1.8 mg/day for 7 days. The slow elimination of colchicine in the presence of renal failure could aggravate the hematologic toxicity in this case.

When administered orally, colchicine is rapidly absorbed from the gastrointestinal tract. It is extensively metabolized in the liver and excreted into bile and urine. Leighton et al. found and studied the effect of hepatic dysfunction and colchicine pharmacokinetics in a bile duct ligation of a rat model. They found that the clearance of colchicine decreased and the terminal half-life was prolonged. The fractional excretion of the unchanged drug in the urine increased. In patients with renal failure, the elimination was markedly decreased. This can potentiate colchicine toxicity even in the therapeutic dosage. Drugs that inhibit microsomal enzyme activity such as cimetidine, erythromycin, tolbutamide and other cytochrome P 450 inhibitors can result in a rise in colchicine blood level and enhance toxicity. Use of these drugs should be cautionary in patient with gout, who usually have associated medical problems.

In conclusion, this case illustrated rare but serious side effects of colchicine in a patient with impaired renal function, who mistakenly increased the dose of the
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Although colchicine is generally considered safe in those with normal renal and hepatic function, it can cause serious side effects in patients with these functions impaired. Physicians should be aware of this condition, particularly in the elderly who have declined renal function.

References
กล้ามเนื้อเป็นพิษจากยาโคลชิซีน : รายงานผู้ป่วย 1 ราย

ศุทธินี ศรีโพธิ์ทอง, น.บ., สุภากรณ์ วังแกว, น.บ., นันทนา กลิตรานท์, น.บ.,
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บทคัดย่อ ผู้ป่วยหญิงไทย อายุ 82 ปี เป็นโรคเก่าแก่ มีอาการท้องร่วง อาเจียน ปวดกล้ามเนื้อและ
กล้ามเนื้อส่วนต้นอ่อนแรงภายหลังที่ผู้ป่วยเพิ่มยาโคลชิซีน ขนาด 0.6 มก. ที่เคยรับประทานวันละ 3
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ภายหลังเข้ารับการรักษาผู้ป่วยในโรงพยาบาล รายงานนี้ได้รวบรวมผลข้อมูลอย่างรุนแรงจากยา
โคลชิซีน และบทคัดย่อขั้นสุดท้ายหรือต้องการเกิดภาวะแทรกซ้อนที่รุนแรงนี้ เชิงในเวชสาร 2547;
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