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Colchicine-Related Polyneuropathy and Multiple Organ Failure

Kolşisin ile İlişkili Polinöropati ve Multi-Organ Yetmezliği

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Summary

Colchicine arrests microtubule assembly and inhibits many cellular functions. This drug is used to treat gout and and Familial Mediterranean Fever. Its gastrointestinal side effects are frequent but more severe adverse effects such as neuropathy and multi-organ failure associated with colchicine are rare. The blood levels of colchicine are dependent on the liver and kidneys. Thus renal or liver failure can result in colchicine toxication. We presented a case of colchicine toxicity, which resulted in multi-organ failure and polyneuropathy. *(Turkish Journal of Neurology 2013; 19:69-71)*

Key Words: Colchicine, polyneuropathy, multi-organ failure

Özet

Kolşisin, mikrotübüllerin oluşumunu engeller ve birçok hücre fonksiyonunu engeller. Bu ilaç gut hastalığı ve Ailevi Akdeniz Ateşi tedavisinde kullanılır. Kolşisin kullanımına bağlı gastrointestinal yan etkiler sıktır, ancak nöropati ve multi organ yetmezliği gibi daha nadir ciddi yan etkileri de vardır. Kolşisinin kan düzeyi böbrek ve karaciğer tarafından belirlendiği için, bu organların fonksiyon bozukluklarında toksisite gelişebilir. Biz bu yazıda kolşisine bağlı multi organ yetmezliği ve polinöropati gelişen bir olguyu sunmaya değer bulduk. *(Türk Nöroloji Dergisi 2013; 19:69-71)*

Anahtar Kelimeler: Kolşisin, polinöropati, multi-organ yetmezliği

Introduction

Colchicine is widely used in attacks of gout arthritis and acute pseudogout, as well as Familial Mediterannean Fever and Behçet disease. The most common side effects of colchicine are nausea, vomiting and diarrhea. It may also cause, although more rarely, fatal multiple organ failure picture including hematologic, cardiac symptoms, neuropathy and myopathy (1). In this case we present a patient developing multiple organ failure and polyneuropathy secondary to colchicine use.

Case

YSeventy-four year-old male patient presented at our clinic with complaints of difficulty in walking, diarrhea, and abdominal pain that started about one month ago, and swelling in hands and feet for the last 15 days. The patient had started colchicine 0.5 mg 2x1 treatment prescribed at another site following a diagnosis of gout approximately 2 months ago. The patient's medical history included hypertension and chronic obstructive pulmonary disease (COPD) in addition to gout, and he was using an angiotensin receptor blocker (ARB) 20 mg 1x1 for hypertension.

Physical examination showed blood pressure and heartbeat to be 130/90 mmHg and 10^2/minute, respectively. His electrocardiogram (ECG) showed sinus tachycardia, and his chest x-ray was normal. His neurological examination showed clear loss of motor strength (2/5) in both lower extremities, and loss of deep tendon reflexes in lower extremities. Sensory examination showed glove-sock hypoesthesia in both upper and lower extremities.

The patient's cranial imaging was normal and the neural conductivity tests and needle electromyography (EMG) examination in the EMG performed with a suspicion of polyneuropathy was consistent with sensorymotor polyneuropathy. Laboratory results showed pancytopenia (Hb=8.9g/dl, WBC=$3.9x10^9$/L, platelet=$84x10^9$/L). Blood chemistry results were as follows: AST

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75.04 U/L (NI=0-35 U /L), ALT 92.48 U/L (NI=0-45), GGT 70 U/L (NI=5-55), LDH 266 U/L (NI=25-248), serum creatine kinase (CPK) 523 U/L (NI=0-171), urea 167 mg/dl (NI=17-43), creatinine 1.66 mg/dl (NI=0.8-1.4), D-dimer 1061ng/ml (NI=0-230), ESR 22 mm/sec. Although the patient's liver function test values were high, there was no unusual findings in the abdominal ultrasonogram (USG). When the patient was evaluated by the pulmonary diseases department due to his COPD history, he was initiated on ipratropium bromide inhaler 6x1 and fluticasone propionate 2x2. Urinalysis showed microscopic hematuria and proteinuria. HBS antigen, hepatitis C antibodies, antinuclear antibody, antiphospholipid antibody, and anticardiolipin values were negative. The patient had an internal diseases clinic consultation due to high values of urea and creatinin, and hypocalcemia, hyponatremia, and hyperphosphatemia. ARB treatment was discontinued, and he was initiated on nifedipin 30 mg 1x1, hydration and electrolyte follow-up was recommended. He had a Physiotherapy and Rehabilitation consultation due to the motor weakness in his lower limbs. He was advised to discontinue colchicine treatment as the weakness might be due to colchicine. Colchicine treatment was discontinued, fluid support was given, blood values were followed daily.

When the patient was seen after two months, his muscle strength had improved to 3-4/5, and he could take a few steps with bilateral support. The other neurological examination findings, however, had not improved.

Discussion

Our patient had gout. Gout is a prevalent disease seen in at least 1% of the world population (2). It develops with the accumulation of urate in joints. The treatment of acute gout arthritis involves colchicine, NSAIIs and corticosteroids (3). Our patient had initiated colchicine for acute gout arthritis.

Colchicine has an inhibiting effect on neutrophiles, especially, at the cellular level. Colchicine is known to have inhibitory effects on phagocytosis and chemotaxis. Colchicine prevents polymerization by binding to the intracellular tubulin protein enabling microtubule formation. In toxic doses it inhibits cell division by arresting mitosis by affecting microtubule functions and chromosomes. These effects are seen in all cells and this explains both the therapeutic and toxic mechanisms. Colchicine has a narrow therapeutic index. The therapeutic and toxic dose intervals are close and toxicity signs present in acute, subacute and chronic stages. The rate of protein binding in therapeutic doses is 10-50% and volume of distribution varies between 2 and 12 L/kg; however this value may go up to 21 L/kg in toxic doses. Colchicine is metabolized in the liver and excreted via kidneys and biliary route. The risk of intoxication in patients with liver and kidney failure is higher and careful dose adjustment is required in these cases. Colchicine accumulates mostly in the bone marrow, liver, kidneys, spleen, heart, lungs, gastrointestinal system and brain (1).

Colchicine intoxication is observed in three stages. In the first stage, gastrointestinal symptoms, leucocytosis, dehidration can be seen in the initial 24 hours. This is followed by the second stage, in 24-36 hours, by multiple organ failure, leucopenia, thrombocytopenia, anemia, liver failure, electrolyte imbalance and disseminated intravascular coagulation. Death may be seen at this stage as a result of cardiac arrhythmias, infections, or hemorrhage (4). Rebound leucocytosis and improvement is seen in the third stage. Myopathy, neuropathy and combined neuromyopathy may be seen following acute intoxication. Proximal muscle weakness, distal areflexia and axonal neuropathy can be seen (5). Our patient also had similar signs including evident widespread muscle weakness, clear decreased sensory perception in bilateral distal regions and loss of reflexes.

As CYP 3A4 enzyme inhibitors increase levels of colchicine, clarithromycine, erithromycine, ketoconazole and natural grapefruit juice may potentially cause colchicine intoxication (6). In addition, concurrent use of colchicine and statins may result in myopathy (7). Our patient was only using an ARB.

There are few reports of fatal cases of colchicine use in literature (8,9,10). Some of these intoxication cases were inadvertently administered, while some were given as treatment. A. A. Tahrani et al. report a case of bone marrow depression, multiple organ failure and death resulting from colchicine use (11). The article reports that the patient has been taking colchicine 1.5 mg/day for two weeks. The clinical picture that started with watery diarrhea and vomiting advanced to multiple organ failure, and resulted in the death of the patient. The authors noted that liver failure developing due to heavy alcohol use and colchicine accumulation may have contributed to the patient's death. Our patient, unlike this case, did not have an alcohol habit or liver disease. Liver and kidney function impairment, as well as pancytopenia was detected as soon as he presented at the hospital. Our patient managed to stay alive as a result of having his metabolic values followed closely and the drug discontinued; in addition, his widespread muscle weakness partially improved with rehabilitation.

Neuromyopathy may be seen in chronic colchicine toxicity, as in the third stage of acute intoxication. Neuromyopathy develops with proximal weakness. Serum creatin kinase level increases (CPK >140 µmol/L) and this condition improves 3-4 weeks after colchicine is discontinued. Chronic toxicity is seen rarely due to most patients' discontinuing the drug because of gastrointestinal side effects. Chronic toxicity is seen in concurrently with impairment of kidney function tests; therefore, it may be interpreted as polymyositis or uremic neuropathy (12).

In conclusion, this case is presented to draw attention to a serious and rare side effect of colchicine, a widely used drug. Rarity of similar cases in literature makes our case valuable. Colchicine is a frequently used drug that may have serious side effects with even low doses. Patients should be instructed to discontinue the drug if they experience gastrointestinal side effects under treatment. Colchicine should be taken in suggested doses, and doses should be carefully adjusted in patients with hepatic and renal failure.

References

1. Finkelstein Y, Aks SE, Hutson JR, Juurlink DN, Nguyen P, Dubnov-Raz G, Pollak U, Koren G, Bentur Y. Colchicine poisoning: the dark side of an ancient drug. Clin Toxicol (Phila) 2010;48:407-414.
2. Terkeltaub RA. Clinical practice. Gout. N Engl J Med 2003;349:1647-1655.
3. Emmerson BT. The management of gout. N Engl J Med 1996;334:445-451.
4. Miller MA, Hung YM, Haller C, Galbo M, Levsky ME. Colchicine-related death presenting as an unknown case of multiple organ failure. J Emerg Med 2005;28: 445-448.
5. Altiparmak MR, Pamuk ON, Pamuk GE, Hamuryudan V, Ataman R, Serdengecti K. Colchicine neuromyopathy: a report of six cases. Clin Exp Rheumatol 2002;20(suppl 4):13-16.

6. Caraco Y, Putterman C, Rahamimov R, Ben-Chetrit E. Acute colchicine intoxication--possible role of erythromycin administration. J Rheumatol 1992;19:494-496.
7. Alayli G, Cengiz K, Canturk F, Durmus D, Akyol Y, Menekse EB. Acute myopathy in a patient with concomitant use of pravastatin and colchicine. Ann Pharmacother 2005;39:1358-1361.
8. Borron SW, Scherrmann JM, Baud FJ. Markedly altered colchicine kinetics in a fatal intoxication: examination of contributing factors. Hum Exp Toxicol 1996;15:885-890.
9. Bonnel RA, Villalba ML, Karwoski CB, Beitz J. Deaths associated with inappropriate intravenous colchicine administration. J Emerg Med 2002;22:385-387.
10. Maxwell MJ, Muthu P, Pritty PE. Accidental colchicine overdose. A case report and literature review. Emerg Med J 2002;19:265-267.
11. Tahrani AA, Sharma S, Macleod A, Moulik P. A case of multi-organ failure. Int J Clin Pract 2007;61:514-516.
12. Kuncl RW, George EB. Toxic neuropathies and myopathies. Curr Opin Neurol 1993;6:695-704.