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□ Case Report □

A Case of High dose Colchicine with No Efficacy in a Patient with Chronic Kidney Disease Taking Rifampicin

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A 54-year-old male on chronic hemodialysis, who was taking rifampicin for tuberculous lymphadenitis, was admitted for an acute gout attack. After administrating 3.6 mg of colchicine for 2 days, symptoms began to alleviate. Despite the relatively high dosage in this end-stage renal disease patient, there were no adverse effects, such as diarrhea, vomiting, or myopathy. After 1 and 6 hours of 0.6 mg colchicine administration, serum colchicine was 1.3930 ng/mL and 0.2464 ng/mL, respectively. These values were lower than the mean concentrations in 13 other patients with chronic kidney disease (CKD) after the same time intervals (4.34±0.56 ng/mL and 1.49±0.15 ng/mL, respectively). As rifampicin is an inducer of cytochrome P450 3A4, metabolism of colchicine had increased. When taking colchicine and rifampicin simultaneously, a higher colchicine dose may be needed for the treatment of acute gout in patients with CKD.

Key Words. **Colchicine, Rifampicin, Acute gout, Renal impairment**

Introduction

Both the incidence and the prevalence of gout are increasing worldwide due to dietary behavior and lifestyle changes. Nevertheless, the treatment for gout remains insufficient. For acute gouty arthritis, the frontline recommended drugs are non-steroidal anti-inflammatory drugs (NSAIDs) and corticosteroid, alone or in combination, in patients with normal kidney function (1). Since NSAIDs can impair kidney function, they have generally been avoided for the treatment of acute gout in patients with chronic kidney disease (CKD). Colchicine or steroids have been the treatment of choice for acute gout in patients with CKD.

A relatively low colchicine dose can affect gout in patients with normal renal function (1,2). The recommended colchicine dosage is 1.2 mg, followed 1 hour later by a further 0.6 mg for the treatment of acute gout in patients with normal renal function (2). However, in patients with CKD, no guidelines have been set by clinical trials, although the recommended colchicine dosage should be lowered.

Here, we report a patient with CKD who displayed no effects for pain and no adverse effects despite a relatively high colchicine dose. To determine the cause, we measured the colchicine concentration in 13 other patients with CKD.

Case Report

A 54-year-old male was admitted to the hospital for evaluation of severe pain in both ankles, metatarsal joint, big toe, and knees. He had end-stage renal disease (ESRD) due to focal segmental glomerulosclerosis and been on chronic hemodialysis therapy. He has been medicated with isoniazid, ethambutol, and rifampicin for the treatment of tuberculous lymphadenitis for 2 weeks before the start of the pain.

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On admission, physical examination revealed a blood pressure of 120/68 mmHg, body temperature of 36.9°C, respiration rate of 20/min, and pulse rate of 78/min. The daily urine output was 300 mL. The review of systems was unremarkable except for multiple joint pain. On physical examinations, both knees, ankles and metatarsal joints evidenced swelling, tenderness and local heat. Laboratory results showed high serum uric acid and impaired kidney function on admission and discharge (Table 1). There were no bacteria in the joint fluid and no growth in cultures of joint fluid. Monosodium urate crystals were evident in the right knee joint fluid. Therefore, he was diagnosed with an acute attack of gout arthritis.

Given the active tuberculosis, we could not use steroids. On the first day, we prescribed a lower dosage of colchicine according to the established guideline. There was no symptom relief. After daily administration of colchicine 1.8 mg for 9 days, there was still no improvement of pain, although there was no adverse effect of colchicine. The colchicine dose was then doubled to 3.6 mg daily. After 2 days of 3.6 mg colchicine administration, the pain began to be relieved. The level of high-sensitivity C reactive protein (CRP) was decreased after taking higher colchicine dose. On day 11 of admission, the level of CRP was decreased from 16.5 to 4.7 mg/dL.

Discussion

Until now, most studies about colchicine and gout treatment have involved patients with normal renal function. A lower colchicine dose (0.6～1.2 mg) is more effective than placebo in treating acute gout flare in patients with normal renal function (3). The Food and Drug Administration-approved dose of oral colchicine, which is effective in the treatment of acute gout attacks, is 1.2 mg followed 1 hour later by a further 0.6 mg in patients with normal renal function. However, little research has been conducted on colchicine dose in patients with CKD. The colchicine dose should be routinely lowered in patients with renal dysfunction (4). Only one recommendation has been published that the use of colchicine should be avoided in patients with creatinine clearance <10 mL/min and in patients receiving hemodialysis (4). Nevertheless, questions remain of why the present high colchicine dose was not effective and why it did not produce adverse effects to this patient. The answer lies in the metabolism of colchicine.

Table 1. Laboratory results on day of admission and 1 day before discharge

	Admission	1 day before discharge
WBC count, /mm^3	12,580	11,140
Hemoglobin, g/dL	10.4	9.8
Hematocrit, %	34.0	32.1
Platelet, /mm^3	143,000	205,000
Total protein, g/dL	6.2	7.8
Albumin, g/dL	2.6	3.2
Total bilirubin, mg/dL	0.5	0.3
ALP, IU/L	61	89
AST (GOT), IU/L	13	19
ALT (GPT), IU/L	2	5
Total cholesterol, IU/L	112	114
Calcium, mg/dL	8.6	8.5
Phosphorus, mg/dL	3.4	4.7
Uric acid, mg/dL	7.7	9.9
CRP, mg/dL	16.5	4.7
BUN, mg/dL	44	37
Creatinine, mg/dL	7.6	9.6

WBC: white blood cell, ALP: Alkaline phosphatase, AST: aspartate aminotransferase, ALT: alanine aminotransferase, BUN: blood urea nitrogen, CRP: C-reactive protein.

Elimination of colchicine occurs by three pathways: renal excretion, metabolism in the liver via the cytochrome P450 3A4 enzyme system and enterohepatic circulation (2,5). In vitro, colchicine is metabolized by cytochrome P450 3A4 and does not inhibit or induce cytochrome P450 3A4 (2). The strong inducers of cytochrome P450 3A4 are anticonvulsants and barbiturates (6). Rifampicin is also a strong inducer of cytochrome P450 3A4 (7). However, isoniazid is a weak inhibitor of cytochrome P450 3A4 (8). Therefore, if they are taken together with colchicines, as in this case, the serum colchicine level would be decreased. After administration of a higher colchicine dose (3.6 mg daily), the symptoms began to be relieved. One and 6 hours after 0.6 mg colchicine administration, the serum colchicine concentration was 1.3930 ng/mL and 0.2464 ng/mL, respectively. The colchicine concentration in this patient was lower than in other patients with CKD after the same time intervals (4.34±0.56 and 1.49±0.15, respectively). In this case, the lower colchicine concentration might be due to rifampicin induction of CYP3A4. Therefore, the treatment was ineffective and induced no toxicity, regardless of the very high colchicine dose. The results indicate that when taking colchicine and rifampicin simultaneously, a relatively high colchicine dose is needed to treat acute gout in patients with CKD.

We also checked the concentration of low dose colchicine by CKD stage in a group of 13 patients (nine men, four women). The estimated glomerular filtration ratio (GFR) was 41.16±4.66 mL/min/1.73 m^2. The peak concentration of colchicine was checked at three points (before administration of colchicine [C0], 1 hour [C1] and 6 hours [C6] after administration of colchicine) (Figure 1). The mean dose of administered colchicine was 0.69±0.06 mg. Eleven patients took 0.6 mg of colchicine and the other two patients took 1.2 mg

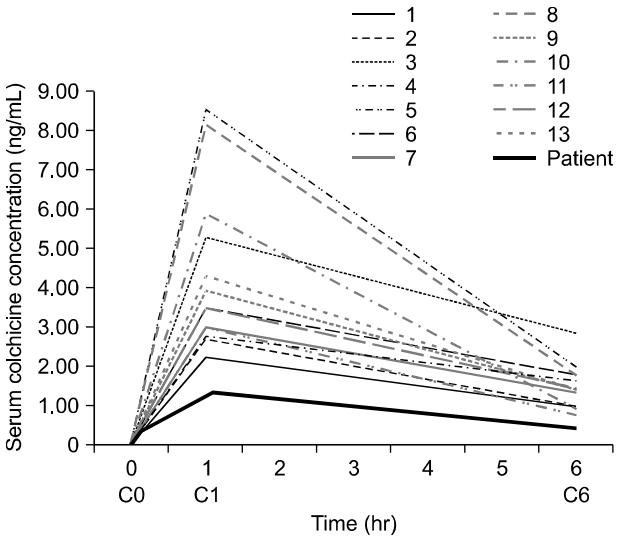

Figure 1. Time dependent serum level of colchicine. In 13 patients, the serum colchicine concentration curve was drawn according to C0, C1 and C6. We assumed that Tmax was an hour after administration. The lowest line shows the result of the case-study patient. Tmax is the time after administration of a drug when the maximum plasma concentration is reached.

of colchicine before sampling. The mean serum colchicine concentration 1 and 6 hours after administration was 4.35±0.56 (range, 2.24～8.51) ng/mL and 1.49±0.15 (range, 0.77～2.82) ng/mL, respectively. The half-life of colchicine was 3.10±0.25 (range, 1.98～5.10) hours. The reported area under the curve (AUC) of colchicine in patients with normal renal function is 0.8 ng/ml/min (48 ng/mL/h) (9). However, the mean AUC of colchicine in our study was 14.78±1.7 ng/mL/min (estimated GFR 38.58±5.03), and the mean normalized AUC (AUC/dose) was 23.27±3.18 (range, 10.03～44.66) mg/min. These were higher than those in patients with normal renal function. A linear relationship was exhibited between the peak colchicine concentration (C1) and CKD classification (p=0.069). Patients with lower estimated GFR could tolerate higher colchicine concentration.

Summary

When taking colchicine and rifampicin simultaneously, a high colchicine dose is needed to treat acute gout in patients with CKD.

Acknowledgments

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