

# Colchicine and NSAID Combination Causing Acute Kidney Injury

Hsuan-Wei Chen<sup>1</sup>, Kuan-Chan Chen<sup>2</sup> and Jin-Shuen Chen<sup>3</sup>

## ABSTRACT

Colchicine is used mainly for the treatment of gout and familial mediterranean fever. The use of colchicine is limited by its toxicity, and colchicine overdose is associated with a high mortality rate. Herein, we are reporting a young man who presented to the emergency department after ingesting 13.5 mg of colchicine and 1200 mg of aceclofenac (non-steroid anti-inflammatory drug) for deliberate self harm. He developed acute kidney injury, metabolic acidosis, and bradycardia after admission. A combination effect of non-steroid anti-inflammatory drug and colchicines was responsible for this event.

**Key words:** Colchicine. NSAID. Acute kidney injury. Toxicity.

## INTRODUCTION

Colchicine is a neutral lipophilic alkaloid with anti-inflammatory activity. It is rapidly absorbed from the gastrointestinal tract and the serum concentrations peak at 0.5 – 3.0 hour after ingestion.<sup>1</sup> The lowest reported lethal doses of colchicine had ever been reported with range from 7 to 26 mg.<sup>2,3</sup> Renal clearance accounts for 5 – 20% of its excretion with the majority of the drug undergoing first pass metabolism and primary deacetylation.<sup>4</sup> Biliary excretion is the chief route of colchicine elimination.<sup>5</sup> Inhibition of microtubule polymerization is the main mechanism of action of colchicine and leads to the disruption of cytoskeleton. With this mechanism, colchicine can inhibit many signaling pathways including intracellular vesicle motility and secretion of endogenous mediators.<sup>6</sup> The complications of colchicine poisoning seen in our case are renal function impairment, cardiac dysrhythmia, and metabolic acidosis. These effects appear in 1 – 7 days after ingesting this drug.<sup>7</sup>

Colchicines and non-steroid anti-inflammatory drug (NSAID) are responsible for acute kidney injury. There are many reports discussing about the NSAID related renal injury and the well-known toxicity of colchicines in kidney toxicity separately. To the authors' knowledge, this is the first case report discussing the combined effects of intoxication from NSAID and colchicine related kidney injury.

## CASE REPORT

A 22-year-old man with history of gouty arthritis treated with colchicine and NSAID called for medical help reporting general malaise, epigastric pain, and frequent watery diarrhea, 48 hours after ingesting a total of 13.5 mg of colchicine (0.20 mg per kilogram of body weight) and 1200 mg of aceclofenac (17.91 mg per kilogram of body weight) for deliberate self harm.

Physical examination revealed a heart rate of 70 beats per minute, blood pressure of 120/90 mmHg, increased bowel sound, non-abdominal palpable mass, and non-rebounding pain. Laboratory examination showed renal insufficiency (blood urea nitrogen/creatinine (BUN/Cr): 21/1.9 mg/dL), metabolic acidosis (pH: 7.31, partial pressure of carbon dioxide (PCO<sub>2</sub>): 36.2 mmHg, and HCO<sub>3</sub><sup>-</sup>: 21.6 mmol/L), normal uric acid (6.4 mg/dL) and unremarkable urinalysis. Electrocardiography showed normal sinus rhythm. One week before presentation, the BUN/Cr was 15/1 mg/dL.

In the Emergency Department, gastric lavage was performed, and activated charcoal was administered orally. Next day after the admission, the arterial blood gas (ABG) values showed pH = 7.3, PCO<sub>2</sub> = 36.6 mmHg, and HCO<sub>3</sub><sup>-</sup>: 18 mmol/L. Elevated BUN/Cr as 32/3.8 mg/dL and decreased urine-output were noted. Due to gradual deteriorated renal function the large amount of fluid hydration (2000 cc per day) was suggested. Followed abdominal sonography showed no hydronephrosis and distended bladder; the post-renal failure was excluded. On the second day of admission, the body weight of this patient was noted to increase by 2.2 kilograms and he developed bradycardia (60 – 70 beats/minute). The BUN/Cr and mean heart beats per minute were recorded as in Figure 1. Furosemide treatment was initiated due to oliguria (daily amount of urine: 250 cc) and the dose was adjusted by the urine output amount. On day 5, the creatinine peaked upto 10.3 mg/dL with 200 cc urine output over a day despite 360 mg furosemide (daily dose) administration.

<sup>1</sup> Department of Internal Medicine, Tri-Service General Hospital, Taipei, Taiwan.

<sup>2</sup> Student, Medical school, National Defense Medical Center, Tri-Service General Hospital, Taipei, Taiwan.

<sup>3</sup> Division of Nephrology, Department of Internal Medicine, Tri-Service General Hospital, Taipei, Taiwan.

Correspondence: Dr. Jin-Shuen Chen, Division of Nephrology, Department of Internal Medicine, Tri-Service General Hospital, Taipei, Taiwan.

E-mail: dgschen@ndmctsg.h.edu.tw

Received January 02, 2012; accepted April 16, 2012.

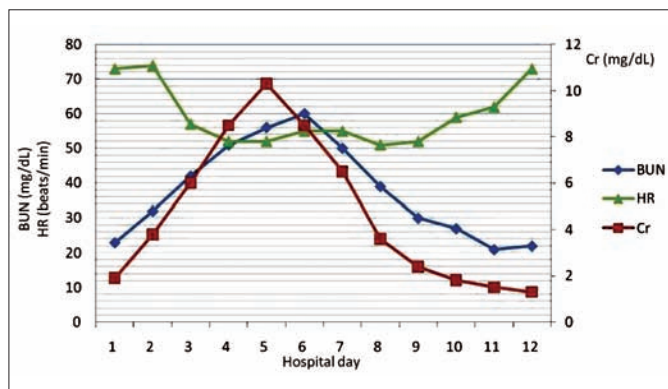


Figure 1: The blood urea nitrogen/creatinine (BUN/Cr) and mean heart beats per minute were recorded. HR: heart rate.

Bradycardia (50 beats per minute) also continued. At this time, ABG analysis showed continued metabolic acidosis (pH = 7.28, PCO<sub>2</sub> = 26.6 mmHg, and HCO<sub>3</sub>: 14 mmol/L). Herein, haemodialysis was arranged on day 5 and day 7. From day 8, the patient started to have greater urine output, the EKG monitoring also showed increased heart beats. Furosemide dose was gradually tapered down: oliguria and bradycardia were eventually resolved. The patient was discharged from the ward on the 12<sup>th</sup> day. At follow-up, 3 months later, there were no sequelae noted.

### DISCUSSION

Colchicine and NSAID are the medications used for the relief of acute severe gout attack. The clinicians often discontinue NSAIDs and decrease the dose of colchicines due to deteriorated renal function. Their combination can strength the treatment effects for acute gouty attack; however, they also increase the risk of acute kidney injury when used in combination. The suggested regimen dose of colchicine in acute gout attack is 1.5 mg in the first 24 hours and should be adjusted with creatinine clearance.<sup>8</sup>

There are two mechanisms of why NSAID would result in acute kidney injury. Firstly, with the inhibition of prostaglandin synthesis from arachidonic acid by blocking of the enzyme cyclooxygenase, NSAID will lead to vasoconstriction resulting in reversible renal ischaemia, a decline in glomerular hydraulic pressure.<sup>9</sup> Secondly, NSAID can induce acute interstitial nephritis which is characterized by T-lymphocytes infiltration and minimal change disease related nephrotic syndrome.<sup>10</sup>

Acute colchicine poisoning is associated with a high mortality rate, and the mainstay of treatment consist of recognition of colchicine poisoning, with, if possible, determination of the dose ingested, early gastrointestinal decontamination, and supportive care. Effective treatment with colchicine-specific Fab fragment antibodies was reported in a single adult patient with colchicine poisoning.<sup>11</sup> *In vitro* studies have shown that colchicine-specific antibodies restore the activity of

tubulin inhibited by colchicines.<sup>12</sup> Presently, this treatment is not commercially available. Clinically, the severity of colchicines toxicity is determined by ingested dose and patient will present with dose-related manifestations.

In this case, the urine concentration was 2 – 3 ug/mL which was 10 – 80 fold higher than plasma; thus the patient's plasma colchicines concentration was 25 – 300 ng/mL. In severe intoxications, plasma levels usually range between 20 – 50 ng/mL. Colchicine overdose can cause hypovolemia due to gastrointestinal symptoms which will lead to hypoperfusion of kidney leading to pre-renal type renal failure. Due to the suppression of microtubular function; the systemic organs will be injured inclusive of kidney (intrinsic cause). The combination effect from these two medicines will result in the synergic effect in renal injury.

A useful diagnostic pearls in the approach to such patients from history and clinical characteristics is summarized in Table I. Usually the agent responsible for acute kidney injury is difficult to distinguish; however, from this table, the physicians can get useful information in evaluating the patients taking overdose of colchicines and NSAIDs.

The combination effect in renal toxicity reinforces the importance of avoiding overdose of these medications and to understand the clinical profiles of these two drugs.

Table I: Overview of NSAID, colchicine related acute renal failure.

	Colchicine	NSAID
History	<ol style="list-style-type: none"> <li>1. Ask specifically about colchicine ingestion.</li> <li>2. Amount ingested and when ingested.</li> </ol>	<ol style="list-style-type: none"> <li>1. Ask specifically about NSAID ingestion.</li> <li>2. Amount, type of NSAID and when ingested.</li> </ol>
Clinical and laboratory features	Severity is directed to ingested dose. <ol style="list-style-type: none"> <li>1. &lt; 0.5 mg/kg "GI symptoms (nausea, vomiting, diarrhea and hypovolemia)". "Decreased amount of coagulation factors".</li> <li>2. 0.5 – 0.5 mg/kg: Multiple organs involved. "GI symptoms, bone marrow suppression, arrhythmia, encephalopathy, renal failure, liver failure, metabolic acidosis, electrolytes imbalance, neuropathy and myopathy".</li> <li>3. &gt; 0.8 mg/kg: Circulatory failure.</li> </ol>	<ol style="list-style-type: none"> <li>1. Usually tolerated in large dose with less toxicity.</li> <li>2. Severe overdose may present as: "GI symptoms: nausea, vomiting". "acid-base unbalance". "massive ingestion (&gt; 400 mg/kg) may cause conscious changes (CNS toxicity)". "coagulopathy". "renal function impairment".</li> </ol>

GI = Gastrointestinal; CNS = Central nerve system; NSAID = Non-steroid anti-inflammatory drug; mg = milligram; kg = kilogram.

### REFERENCES

1. Terkeltaub RA. Colchicine update: 2008. *Semin Arthritis Rheum* 2009; **38**:411-9.
2. Macleod JG, Phillips L. Hypersensitivity to colchicine. *Ann Rheum Dis* 1947; **6**:224-9.
3. Dickinson M, Juneja S. Haematological toxicity of colchicines. *Br J Haematol* 2009; **146**:465.

4. de Lannoy IA, Mandin RS, Silverman M. Renal secretion of vinblastine, vincristine and colchicine *in vivo*. *J Pharmacol Exp Ther* 1994; **268**:388-95.
5. Niel E, Scherrmann JM. Colchicine today. *Joint Bone Spine* 2006; **73**:672-8.
6. Yang H, Ganguly A, Cabral F. Inhibition of cell migration and cell division correlates with distinct effects of microtubule inhibiting drugs. *J Biol Chem* 2010; **285**: 32242-50.
7. Finkelstein Y, Aks SE, Hutson JR, Juurlink DN, Nguyen P, Dubnov-Raz G, *et al*. Colchicine poisoning: the dark side of an ancient drug. *Clin Toxicol* 2010; **48**:407-14.
8. Terkeltaub RA. Clinical practice. Gout. *N Engl J Med* 2003; **349**: 1647-55.
9. Murray, MD, Brater, DC. Renal toxicity of the non-steroidal anti-inflammatory drugs. *Annu Rev Pharmacol Toxicol* 1993; **33**:435.
10. Musu M, Finco G, Antonucci R, Polati E, Sanna D, Evangelista M, *et al*. Acute nephrotoxicity of NSAID from the foetus to the adult. *Eur Rev Med Pharmacol Sci* 2011; **15**:1461-72.
11. Baud FJ, Sabouraud A, Vicaut E, Taboulet P, Lang J, Bismuth C, *et al*. Brief report: treatment of severe colchicines overdose with colchicine-specific Fab fragments. *N Engl J Med* 1995; **332**: 642-5.
12. Rouan SK, Otterness IG, Cunningham AC, Holden HE, Rhodes CT. Reversal of colchicine-induced mitotic arrest in Chinese hamster cells with a colchicine-specific monoclonal antibody. *Am J Pathol* 1990; **137**:779-87.

