Colchicine overdose with coingestion of nonsteroidal antiinflammatory drugs

Anjuli Little, MD, BSc*; David Tung, PharmD†; Christine Truong, BScPharm‡; Stephen Lapinsky, MD*; Lisa Burry, BScPharm, PharmD§

ABSTRACT
Colchicine has a low therapeutic index. Its toxic effects generally occur at doses ≥ 0.5 mg/kg. We present the case of a 39-year-old female with toxicity following ingestion of 0.28 mg/kg. The patient presented to the emergency department (ED) with severe nausea, vomiting, and abdominal pain following an intentional multidrug ingestion that included colchicine, indomethacin, and zopiclone. Despite toxicologic management and supportive care, admission to the intensive care unit was required for clinical deterioration and symptom management. Shock and multiorgan failure resulted, with death occurring 52 hours postingestion. Although the toxic effects of colchicine are well documented, mortality caused by low doses is relatively uncommon. Management of toxicity consists of early diagnosis, decontamination, and supportive measures. Toxicity may be enhanced by drug interactions inhibiting metabolic enzymes or poor excretion due to renal failure. In this case, the ingestion of a nonsteroidal antiinflammatory drug and the associated volume depletion from the gastrointestinal effects of colchicine may have contributed to renal dysfunction, exacerbating the toxicity of colchicine. This ingestion of a relatively small dose of colchicine led to severe toxicity. Treatment options for colchicine toxicity are limited.

Keywords: coingestion, colchicine, nonsteroidal antiinflammatory drug, overdose

Colchicine, an alkaloid extracted from the plants Colchicine autumnale (autumn crocus) and Gloriosa superba (glory lily), has been used to treat gout for almost 1,500 years. Colchicine interferes with cellular 

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Administration of colchicine with inhibitors of CYP3A4 and/or P-gp may exacerbate toxicity. Drug clearance is reduced in those with renal and/or hepatic insufficiency.

Widespread use of colchicine is limited by its recognized toxicity, even though the literature about clinical toxicity is limited. Overdose is difficult to manage as there is no antidote. Toxicity has been reported with doses \( \geq 0.5 \text{ mg/kg} \), with death possible when ingestion exceeds 0.8 mg/kg. We present a case of a fatal multidrug overdose after ingestion of a 25 mg (0.28 mg/kg) dose of colchicine.

**CASE SUMMARY**

A 39-year-old, 90 kg female presented to the emergency department (ED) at 4:00 am with severe nausea, vomiting, abdominal pain, and diarrhea following the intentional ingestion of multiple medications. The patient’s husband reported that the couple went to bed at 12:00 am. He found his wife vomiting tablets at 2:00 am. He noted that she had ingested his medications: 40 tablets of colchicine (25 mg or 0.28 mg/kg), 50 tablets of indomethacin (1.25 g), and 10 tablets of zopiclone (75 mg). The patient reported use of personal medications (topiramate, valproic acid, olanzapine, lorazepam, levotheroxine, oxycodeone, furosemide, omeprazole) prior to admission but was unable to specify timing or doses. The patient denied use of over-the-counter or herbal medications. Her past medical history was significant for bipolar affective disorder, hypothyroidism, reflux disease, multiple suicide attempts involving multidrug overdose, and illicit drug use.

The ED admission vital signs are shown in Table 1. Preliminary bloodwork revealed increased white blood cells (WBCs) with a normal platelet count. Serum creatinine was elevated (Table 2), whereas other investigations found a serum lactate of 0.86 mmol/L, an international normalized ratio (INR) of 2.4, and a troponin T of 0.02 (normal < 0.01). Urine toxicology screening was negative except for benzodiazepines. Alcohol, salicylate, and acetaminophen levels were negative. The electrocardiogram (ECG) and chest radiograph were normal.

Preliminary management included administration of two doses of activated charcoal (50 g) and intravenous (IV) hydration of a total 6 L NaCl 0.9% over 6 hours with 4 L by bolus because of hemodynamic compromise at 6 hours postingestion (see Table 1). Repeat urine toxicology screening remained negative for alcohols, salicylates, and acetaminophen and was negative for cocaine, cannabinoids, opiates, amphetamines, and barbiturates.

Approximately 8 hours postingestion, the patient remained alert and oriented. Worsening vital signs (see Table 1), severe shortness of breath, and abdominal pain requiring intermittent IV fentanyl prompted transfer to the intensive care unit (ICU). As per the advice of the Ontario Poison Centre, she received multidose activated charcoal (MDAC) for enhanced elimination, additional fluid boluses, and vitamin K (10 mg by IV) due to the elevated INR. At 18 hours postingestion, vital signs continued to worsen (see Table 1), with reduced urine output (see Table 2). Arterial blood gases demonstrated metabolic acidosis: pH 7.20, carbon dioxide partial pressure 14.9 mm Hg, and bicarbonate 6.6 mEq/L. The patient was intubated. An IV norepinephrine infusion titrated to maintain mean arterial pressure (MAP) \( \geq 60 \text{ mm Hg} \) was started. She received 100 mEq NaHCO\(_3\) IV and 400 \( \mu \text{g} \) phenylephrine IV.

Over the next 24 hours, WBC and platelet counts declined (see Table 2). At 28 hours postingestion, her

<table>
<thead>
<tr>
<th>Postingestion time (h)</th>
<th>Blood pressure (mm Hg)</th>
<th>Heart rate (bpm)</th>
<th>Respiratory rate (per min)</th>
<th>Temperature, °C (°F)</th>
<th>Mean arterial pressure (mm Hg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>2</td>
<td>143/49</td>
<td>77</td>
<td>24</td>
<td>34.7 (94.4)</td>
<td></td>
</tr>
<tr>
<td>6</td>
<td>70/50</td>
<td>110</td>
<td>30</td>
<td></td>
<td></td>
</tr>
<tr>
<td>8</td>
<td>116/78</td>
<td>106</td>
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<td>36.7 (98)</td>
<td>100</td>
</tr>
<tr>
<td>18</td>
<td>90/50</td>
<td>130</td>
<td>41</td>
<td></td>
<td>65</td>
</tr>
<tr>
<td>28</td>
<td>80/58</td>
<td>135</td>
<td>45</td>
<td>39.9 (103.8)</td>
<td>70</td>
</tr>
<tr>
<td>35</td>
<td>98/61</td>
<td>142</td>
<td>45</td>
<td>39.8 (103.6)</td>
<td>75</td>
</tr>
<tr>
<td>50</td>
<td>86/51</td>
<td>143</td>
<td>40</td>
<td>40.0 (104)</td>
<td>65</td>
</tr>
<tr>
<td>52</td>
<td>30/27</td>
<td>96</td>
<td>40</td>
<td>40.0 (104)</td>
<td>28</td>
</tr>
</tbody>
</table>
condition deteriorated further (see Table 1) despite continuous fluid resuscitation and an increasing rate of norepinephrine infusion. A bicarbonate infusion was initiated. MDAC was continued—50 g charcoal in sorbitol alternating with 50 g in water every 2 hours. Further blood work revealed worsening serum creatinine levels (see Table 2).

Continuous IV infusions of midazolam and morphine were initiated at 35 hours postingestion for severe pain, agitation, and respiratory distress not relieved with hourly IV fentanyl (100 μg). Further doses of bolus IV fluid replacement were required to maintain MAP $\geq 60$ mm Hg. A dose of granulocyte colony-stimulating factor (G-CSF) (480 μg IV) was given in response to the drop in WBCs to 2.79 $\times 10^3$/μL, and the patient received 5 units of platelets and 1 unit of packed red blood cells. No growth occurred in urine, sputum, and blood cultures taken in the ED. The patient remained febrile, with poor vital signs (see Table 1). A subsequent chest radiograph revealed significant left lower lung infiltrates. An abdominal radiograph showed no evidence of perforation. Treatment with piperacillin/tazobactam 3.375 mg IV was administered at this point for febrile neutropenia and probable septic shock. Rifampin 600 mg IV was given in an attempt to induce the metabolism of colchicine.

Despite aggressive management, the patient remained tachycardic, tachypneic, and febrile, with hypotension unresponsive to fluids and a low WBC count (see Table 1 and Table 2). Nitric oxide inhalation and neuromuscular blockade with 15 mg IV bolus followed by a 20 mg/h infusion of cisatracurium were initiated to control worsening ventilation, without effect. The patient succumbed to multiorgan failure 52 hours postingestion.

### DISCUSSION

Recommendations for the management of colchicine poisoning include GI decontamination and aggressive supportive measures. Investigations should include basic bloodwork, chest radiography, urinalysis, continuous ECG monitoring, and toxicology screening. Diagnosis of colchicine overdose is based on a three-stage clinical presentation and documented ingestion history. Stage 1 includes nausea, vomiting, profuse diarrhea, and abdominal pain associated with hypovolemia and leukocytosis. Typical onset is 2 to 8 hours postingestion and lasts from 24 to 48 hours. Stage 2 is marked by the development of multiorgan failure with metabolic derangements, occurring 1 to 7 days postingestion. Cardiac arrhythmias, acute respiratory distress syndrome, renal failure, electrolyte disturbances, bone marrow suppression, and coagulopathies are all frequent manifestations. Death is commonly due to hemodynamic collapse, cardiac arrhythmias, and infectious or hemorrhagic complications.

Stage 3 for survivors is recovery. This occurs 7 to 21 days postingestion with resolution of organ system derangements and recovery of bone marrow function. For early ingestions, use of gastric lavage and activated charcoal may be beneficial. Enhanced elimination with MDAC should be considered due to colchicine’s enterohepatic recirculation. This is especially true for potentially lethal ingestions as no methods of extracorporeal elimination are useful for this drug.

Supportive care should take place in an ICU due to the high probability risk of deterioration and septic shock. The use of vasopressor and antiarrhythmic medications may be indicated. Mechanical ventilation

<table>
<thead>
<tr>
<th>Postingestion time (h)</th>
<th>WBCs ($\times 10^3$/μL)</th>
<th>Platelets ($\times 10^3$/μL)</th>
<th>AST (IU/L)</th>
<th>ALT (IU/L)</th>
<th>CK (IU/L)</th>
<th>SCr (μmol/L)</th>
<th>Urine output (mL/h)</th>
</tr>
</thead>
<tbody>
<tr>
<td>3</td>
<td>46.36</td>
<td>359</td>
<td></td>
<td></td>
<td>275</td>
<td>292</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>39.29</td>
<td>320</td>
<td>200</td>
<td>30</td>
<td>209</td>
<td>310</td>
<td></td>
</tr>
<tr>
<td>18</td>
<td>30.75</td>
<td>207</td>
<td>469</td>
<td>165</td>
<td>288</td>
<td>301</td>
<td>12</td>
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<tr>
<td>21</td>
<td>24.27</td>
<td>150</td>
<td>801</td>
<td>345</td>
<td>364</td>
<td>274</td>
<td>12</td>
</tr>
<tr>
<td>28</td>
<td>9.26</td>
<td>104</td>
<td>3,420</td>
<td>1,050</td>
<td>3,740</td>
<td>292</td>
<td>12</td>
</tr>
<tr>
<td>35</td>
<td>2.79</td>
<td>39</td>
<td></td>
<td></td>
<td></td>
<td>274</td>
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</tr>
<tr>
<td>45</td>
<td>0.54</td>
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<td>3,470</td>
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<td>10</td>
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<td>0.29</td>
<td>81</td>
<td>3,650</td>
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<td>4,640</td>
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<tr>
<td>50</td>
<td>0.31</td>
<td>69</td>
<td>4,100</td>
<td>982</td>
<td>5,840</td>
<td>380</td>
<td>&lt;10</td>
</tr>
</tbody>
</table>

ALT = alanine aminotransferase; AST = aspartate aminotransferase; CK = creatine kinase; SCr = serum creatinine; WBC = white blood cell.
should be considered for respiratory compromise, and broad-spectrum antibiotics will be required for febrile patients.\textsuperscript{15,16} In our case, activated charcoal was given as part of an overdose regimen for colchicine and all coingested medications. G-CSF, rifampin, and supportive measures were suggested by the Ontario Poison Centre to treat the worsening clinical presentation of the patient. At least eight case reports have shown successful use of G-CSF in shortening the duration of neutropenia following colchicine overdose.\textsuperscript{14,18} Harris and colleagues described three cases where G-CSF was administered on day 4 or 5 post-ingestion.\textsuperscript{14} Following 2 to 3 days of daily dosing, WBCs began to recover and platelet levels improved. In our case, WBC and platelets exhibited a fourfold decline 28 hours post-ingestion. Consequently, the single dose of G-CSF 480 µg (5 µg/kg) was administered much earlier on day 2 post-ingestion. Administration of rifampin has been theorized to promote the excretion of colchicine via P-gp induction and increased metabolism by CYP3A4.\textsuperscript{26-28} No case reports attempting this treatment were found. In our case, 600 mg IV rifampin was given, with no obvious improvement. It remains uncertain whether earlier administration would have impacted this case.

Based on the history provided, our patient consumed a relatively small dose of colchicine yet experienced lethal toxic effects, developing early-onset acute renal failure (ARF). Although unusual, this was similar to a case of a 37-year-old woman who presented after ingesting 15 mg colchicine with severe toxicity suggested to be associated with early ARF.\textsuperscript{12} Volume depletion is a serious side effect of colchicine intoxication and is often a fundamental cause of ARF.\textsuperscript{12} Our patient ingested multiple medications, including indomethacin, prompting us to consider the additive renal toxicity seen with nonsteroidal antiinflammatory drugs (NSAIDs) as a causative factor in her early-onset ARF. The evidence suggests that indomethacin toxicity can result in ARF alone or in the presence of volume depletion.\textsuperscript{21-26} One case described a 47-year-old man who suffered ARF post-ingestion of 20 mg (0.22 mg/kg) of colchicine with 600 mg of indomethacin.\textsuperscript{26} ARF was attributed to the overdose of colchicine due to various factors, principally volume depletion. The authors stated that it was probable that indomethacin had a role in the development of ARF, potentially a result of kidney tubular damage due to indomethacin’s inhibition of prostaglandin synthesis, which hinders efferent arteriolar vasodilation. Support for this theory was outlined by Venturini and colleagues, who described ARF in a small subset of patients taking NSAIDs, particularly in already volume-depleted patients.\textsuperscript{27}

CONCLUSIONS

Colchicine toxicity is rare and can be life-threatening, requiring timely clinical recognition and management. The role of aggressive fluid resuscitation needs to be highlighted as our patient’s fatal outcome may have resulted from early development of renal failure brought on by a combination of factors, including septic shock and hypovolemia with concomitant NSAID consumption.

Competing interests: None declared.

REFERENCES


