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CASE REPORT

Accidental Plant Poisoning with *Colchicum autumnale:* Report of Two Cases

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Colchicine poisoning is a rare but serious and potentially fatal event which results from food poisoning or overdose with drugs containing colchicine, with no currently available antidote. We report two cases of plant poisoning with *Colchicum autumnale*, in which the patients had identical initial symptoms but developed extremely different clinical courses. One patient recovered after only moderate gastroenteritis and liver injury, whereas the other died of rapid progressive multiple organ failure 52 h after the plant ingestion. We recommend that all patients suspected of colchicine intoxication due to its unpredictable outcome should be managed according to the principles of intensive care, irrespective of the actual degree of poisoning.

Key words: *alkaloids; colchicine; diarrhea; multiple organ failure; plant poisoning; plants, medicinal; toxicology*

Colchicine is an alkaloid derived from *Colchicum autumnale*, a member of the family *Liliaceae* and commonly known as the autumn crocus, wild saffron, meadow saffron, naked lady, and son-before-the-father. All parts of the plant are poisonous and contain colchicines, but the highest concentration of the alkaloid is found in the corm or underground bulb (1). Extracts from this plant have been known to be poisonous for over 2000 years. Since 6th century AD, the extract, colchicum, has been used in medicine as a drug for treatment of podagra or gouty arthritis (1).

Colchicine poisoning (2) is a rare but serious and highly fatal event that occurs as a result of either a colchicine-containing drug overdose (3) or, more rarely, food poisoning from plants containing this alkaloid (4). The signs of toxicity follow a predictable course and require both early recognition and aggressive supportive care to increase the patient's chances for survival (2,3). There are no available antidotes; anti-colchicine antibodies have been studied, but are still unavailable for human use (5). Death results from multiorgan failure (6). In this study, we present two cases of *Colchicum autumnale* food poisoning, which had similar initial phase, but very different clinical course and outcome.

Case Reports

In May 2000, a married couple living in Mrkopalj, a town in Gorski Kotar, Croatia, consumed a salad of crude vegetables presumed to be wild garlic *(Allium ursinum)*, a plant having antihypertensive and other salutary effects. They had eaten the same vegetable several times before. However, at that particular time, the wife felt that the salad tasted differently and stopped eating it, while her husband continued. After an hour, both developed symptoms of abdominal pain and vomiting, which were soon followed by diarrhea. They were admitted to our institution 36 h after the salad ingestion and presented with very different clinical courses.

Case No. 1

The 60-year-old woman complained of vomiting, diarrhea, and abdominal discomfort. She had a history of arterial hypertension, which she treated regularly with daily doses of lisinopril, an angiotensin converting enzyme inhibitor. On admission, her Glasgow Coma Scale score was 15, pulse rate 60/min, blood pressure 170/80 mm Hg, respiratory rate 16/min, and body temperature 36.8 °C. Her abdomen was slightly tender, liver and spleen nonpalpable. Laboratory findings were as follows: erythrocytes 4.02×10^{12}/L; hemoglobin 111 g/L; white blood cells 4.4×10^{9}/L, with normal differential count; platelets 98×10^{9}/L (normal range, 150-350), Na^+ 134 mmol/L (normal range, 133-147), K^+ 2.8 mmol/L (normal range, 3.8-5.1), urea 14.3 mmol/L (normal range, 1.7-7.5), creatinine 170 μmol/L (normal range, 40-120), blood glucose 4.2 mmol/L (normal range, 3.9-6.1), total bilirubin 15 μmol/L (normal range, <17), aspartate transaminase (AST) 112 IU/L (normal range, <31), alanine transaminase (ALT) 47 IU/L (normal range, <31), γ-glutamyl transpeptidase (γ-GT) 51 IU/L (normal range, <32), alkaline phosphatase (AP) 104 IU/L (normal range, <104), lactate dehydrogenase (LDH) 481 IU/L (normal range, 135-225), creatine kinase (CK) 543 IU/L (normal range, <145), CK-MB isoenzyme 36 IU/L (normal

range, 6% of total CK), serum amylase 55 IU/L (normal range, <90), and prothrombin time 96% of normal activity. Urinalysis was normal, with negative myoglobin. Electrocardiogram showed a sinus rhythm with right bundle branch block. Chest X-ray was normal. Abdominal ultrasound revealed uneven and increased liver echogenicity, and cortical widening and decreased echogenicity of the kidneys.The patient was rehydrated and electrolyte deficits were corrected with lisinopril dose of 20 mg. Liver enzymes, signaling an ongoing injury, were elevated for 3 more days. High values of extracardiac CK were observed as well, but with negative urinary myoglobin. Platelet count was stable. After a week, all parameters gradually improved and the patient become stable with no complaint. Lisinopril was continued at an increased dose throughout the hospitalization. The woman was discharged after 2 weeks. On subsequent visits, both clinical and laboratory findings were within normal values.

Case No. 2

The 64-year-old man, without significant past medical history, presented with circulatory compromise, respiratory distress, and lethargy. He experienced a particularly severe form of gastrointestinal irritation and reported some 300 episodes of vomiting during the preceding 36 h. His Glasgow Coma Scale score was 13, pulse rate 112/min, blood pressure 80/40 mm Hg, respiratory rate 24/min, and body temperature 36.2 ºC. He was cyanotic, dehydrated, and anuric, with distended abdomen and absent bowel sounds. Laboratory values were the following: hemoglobin 164 g/L, hematocrit 49%, white blood cells $7.1x10^9$/L, platelets $30x10^9$/L, Na^+ 130 mmol/L, K^+ 4.2 mmol/L, urea 8.0 mmol/L, creatinine 416 μmol/L, blood glucose 2.7 mmol/L, AST 491 IU/L, ALT 125 IU/L, serum amylase 167 IU/L, pH 7.16 (normal range, 7.35–7.45), PaO_2 10,5 kPa (normal range, 10-12), $PaCO_2$ 3.8 kPa (normal range, 4.7-6.0), HCO_3^- 10.2 mmol/L (normal range, 18-30), and 92% arterial oxygen saturation (normal range, 95-100%) were observed. Urinalysis showed 1+ proteins and fine granular casts on sediment examination.

The patient was admitted to the intensive care unit because of hypotension and metabolic acidosis. After initial volume expansion and dopamine infusion, the patient's blood pressure stabilized. However, administration of bicarbonate had little, if any, effect on acidosis, the patient remained anuric despite the therapy with fluids and diuretics. Three hours after being admitted to the intensive care unit, the patient developed acute respiratory failure, requiring intubation and assisted mechanical ventilation. Acidosis was unresponsive to repeated doses of bicarbonate and standard ventilatory support. Central venous pressure progressively increased, and in the 4th h after admission, a bout of hypotension occurred. It was successfully managed with increased doses of dopamine and noradrenaline. Coagulation tests revealed immeasurable values, so 500 mL of fresh frozen plasma was administered in the 7th hour. Thereafter, prothrombin time measured 30% of normal activity and partial thromboplastin time was 59 s. The patient was relatively stable until the irreversible cardiovascular collapse occurred during the 16th hour. His pulse rate was 99/min, mean arterial pressure 118 mm Hg, and central venous pressure +27 mm Hg. Reanimation was unsuccessful. Laboratory findings from the blood drawn during the period of reanimation showed the following: glucose 0.9 mmol/L, pH 7.15, PaO_2 29.0 kPa, $PaCO_2$ 3.6 kPa, HCO_3^- 9.6 mmol/L, arterial oxygen saturation 100%, Na^+ 142 mmol/L, K^+ 4.2 mmol/L, urea 25 mmol/L, creatinine 430 μmol/L, white blood cells $1.8x10^9$/L, platelets $19x10^9$/L, hemoglobin 111 g/L, and hematocrit 32%.

Autopsy revealed hypocellular bone marrow, widespread hepatic and renal necrotic changes, and congestion, hemorrhage, transudate, epithelial detachment, and necroses in the lungs. Hemorrhages, necroses, congested mesenterial capillaries and swollen, hemorrhagic mesenterial lymph nodes were also observed along the digestive tube. Gastrointestinal lesions contained a peculiar cytological pattern abundant in mitotic figures.Forensic investigation revealed the presence of colchicine and related alkaloids in the remnants of the salad the patient consumed. The substance was not found in the postmortem analysis of homogenized blood, bile, liver, and kidney tissue, and neither was alcohol. Based on the obvious similarity between the two vegetables, presumed *Allium ursinum* and the ingested *Colchicum autumnale*, and the fact that the patients did not have enough discriminative skills to discern between them, the fatal case was concluded as an accidental death.

Discussion

In the cases reported, the wife survived and the husband succumbed to the accidental poisoning with colchicine. The source of colchicine was *Colchicium autumnale,* and both patients had eaten the same plant at the same time. Although the wife was on ACE inhibitor lisinopril for the management of hypertension, and the husband was not, the possible protective effect of the ACE inhibitor cannot be considered on the basis of data available, because the two patients differed in their anthropometric variables (man's weight: 100 kg, height: 175 cm; woman's weight: 68 kg, height: 165 cm), comorbidity, and, most important, the amount of poisonous plant ingested. Both expressed identical initial symptoms, but very different clinical courses thereafter. The woman's laboratory findings showed low serum potassium and platelet count with moderately elevated creatinine, transaminases, and CK. Liver, renal, and bone marrow involvement were evident, but her recovery was rapid and complete. In contrast, the man had very low platelet count, decreased prothrombin time, low serum glucose and sodium levels, elevated transaminase, and severe acidosis. He developed respiratory, renal, bone marrow, and liver failure and died from cardiovascular collapse 52 h from ingestion.

The fact that colchicine was not detected in the patient's blood obtained postmortem can be explained by the short pharmacokinetic half-life of that substance, which ranges from 12 to 30 minutes (7,8). Colchicine is metabolized by deacetylation in the

liver; 10-25% of the unchanged drug and its metabolites are excreted into the bile and undergo entero-hepatic recirculation (9,10). Thus, the diagnosis of colchicine poisoning was established postmortem by detection of the substance in the remnants of consumed salad. Colchicine poisoning is most often the consequence of drug overdose during the therapy of gouty arthritis and familial Mediterranean fever (3). On the other hand, poisoning by ingestion of *Colchicum autumnale*, a plant containing this alkaloid, is far more rarely reported (4). Toxicity expression may be delayed until 2 to 12 h postingestion. It first manifests as a severe form of gastrointestinal irritation (nausea, vomiting, abdominal pain, and hemorrhagic gastroenteritis), which then evolves into a multisystem failure 24 to 72 h postingestion (3). Fever, neurological (confusion, coma, ascending peripheral neuropathy), cardiovascular, pulmonary, renal, hepatic, and hematological (marrow depression, coagulation disorder) manifestations are all inclusive (3). Death, which commonly results within 7 to 36 h, is caused by respiratory failure, cardiovascular collapse, or sudden asystole. If death occurs on the 3rd to 7th day of poisoning, the cause is usually septic shock. In mild cases of poisoning, the recovery can be seen 7 to 10 days after ingestion (1).

One of the several mechanisms of colchicine toxicity is that it binds selectively and reversibly to 65 subunits of microtubules, altering thus cellular processes such as cell shaping, division, mobility, and ability to exhibit phagocytosis (11). Other mechanisms, unrelated to binding microtubules, have also been described (12). Clear distinction between nontoxic, toxic, and lethal doses of colchicine do not seem to exist (13). Some authors report that colchicine ingestion up to 0.5 mg/kg is not fatal in contrast to that of over 0.8 mg/kg (14).

The therapy consists of surveillance, supportive therapy, and lavage of the stomach, which is of benefit only shortly after the ingestion. In the future, however, a strategy involving monoclonal antibodies might considerably improve the prognosis and thus make an early diagnosis even more important (15).

In the case of colchicine poisoning, the clinical picture will seldom point to the etiology of the disease. Diagnosis of colchicine intoxications should be suspected in circumstances where consumption of wild vegetables has been reported in conjunction with a strong gastrointestinal symptoms and/or evidence of multiple system affection. We can suspect poisoning with *Colchicum autumnale* particularly in cases where wild garlic (Allium *ursinum*) consumption is mentioned. Although the etiological diagnosis does not implicate specific measures in the management of the poisoning, it determines the pattern of medical approach, which must include early intensive support measures irrespective of the expressed level of toxicity.

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