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Colchicine Intoxication Subsequent to an Autolytic Attempt with Positive Evolution

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Abstract

Background and objectives: Colchicine is a drug that has been used to treat gout for several centuries, it is also indicated in certain autoimmune diseases and has been tested as a chemotherapeutic. Only a few cases of intoxication by this drug have been described, but it is known that it has a narrow therapeutic margin (0.5 to 0.8 mg/kg), almost always resulting in fatal results above these limits. Regarding therapeutic management, the initiation of supportive measures is essential. Initial strategies are gastric lavage, administration of activated charcoal and fluid resuscitation aimed at preventing renal failure.

Case report: A 63-year-old man with a history of spondylodiscitis and gouty arthropathy, receiving colchicine treatment. He reported abdominal symptoms with nausea, vomiting, watery stools, and diffuse pain after taking 36 tablets of 1 mg of colchicine due to exacerbation of arthralgias (the patient later recognized the autolytic ideation). He was hospitalized in the ICU due to hemodynamic instability, severe pancytopenia, respiratory failure requiring mechanical ventilation and non-oliguric acute renal failure. The patient improved and was discharged from the ICU after 14 days.

Conclusions: Colchicine poisoning is rare and has high mortality despite the favorable evolution of our patient. There is no specific treatment at the moment and management should emphasize early admission to the ICU, close monitoring and organ support measures.

Keywords: Colchicine, Intoxication, Autolytic

Introduction

Colchicine is an anti-inflammatory drug widely used to treat gout for several centuries. It is extracted from a plant called *Colchium autumnale* [1]. Its mechanism of action consists of the reversible inhibition of tubulin, a protein that forms part of the cell cytoskeleton involved in inhibiting processes such as cell mitosis, phagocytosis, or the secretion of endoplasmic vesicles [2], among others, and it is therefore also used in the treatment of autoimmune diseases and has been tested as a chemotherapeutic [3].

We report a case of colchicine intoxication subsequent to an autolytic attempt with favorable evolution, with ingestion of 0.55 mg/kg (36 mg/65 kg).

Case Report

A 63-year-old male patient with a relevant personal history of spondylodiscitis and long-standing chronic arthropathy suggestive of gouty arthropathy, under treatment with colchicine (1 mg/day) and allopurinol (300 mg/day), with multiple admissions to Internal Medicine for polyarticular gouty arthritis, probably due to improper adherence to treatment.

The patient arrived at the emergency room (ER) with nausea, vomits, watery stools and diffuse abdominal pain after taking 36 tablets of 1 mg of colchicine due to exacerbation of arthralgias (the patient later recognized the autolytic ideation). Laboratory tests showed: venous lactate 8 mmol/L, pH 7.5 and

pCO2 20 mmHg, the rest without alterations. Symptomatic treatment was started (antiemetic, hydration, proton pump inhibitors).

Twenty-four hours later, he presented analytical deterioration (creatinine 1.57 mg/dL, potassium 5.4 mmol/L, arterial lactate 7.2 mmol/L, pH 7.39, pCO2 19 mmHg, bicarbonate 11.5 mmol/L, INR 2, prothrombin activity 42%), remaining clinically stable, although with a tendency to arterial hypotension (90/45 mmHg), leading to a UCI admission.

Low-dose vasoactive support was required during the first hours, with progressive improvement of hyperlactacidemia until its correction.

The patient developed severe pancytopenia on admission with leukopenia up to 0.29 x 10^3/µL (neutrophils 0.1 10^3/µL), hemoglobin 8.3 g/dL and plateletopenia 12 x 10^3/µL. The patient was treated with colony stimulating factor for two days, showing marrow recovery from the ninth day, with reactive leukocytosis of 27 x 10^3/µL.

Respiratory worsening since admission with increased need for FiO2 and mismanagement of secretions, requiring orotracheal intubation and mechanical ventilation on the fourth day, and extubation after 11 days, with no further incidents.

Empirical antibiotherapy with levofloxacin, ceftriaxone and oseltamivir was started due to suspicion of respiratory infection, escalating to broad-spectrum antibiotherapy due to elevated acute phase reactants. Microbiological results were positive for influenza A (PCR in pharyngeal exudate) and oxicillin-resistant *Staphylococcus aureus* (in pharyngeal exudate).

The patient presented diarrhea in the first days of admission, with growth of *Campylobacter* spp. in stool culture, which was progressively resolved. He also developed alteration of liver function with mild hypertransaminasemia, bilirubin of 2.2 mg/dl and lactate dehydrogenase (LDH) 3000 U/L. Elevation of myocardial damage markers without associated clinical symptoms and normal echocardiogram.

Acute non-oliguric renal failure and metabolic acidosis appeared, which improved after intensive serum therapy, with an increase of creatinine kinase (CK) up to 2200 U/L. The patient was presented with temporary alopecia in the last days of admission. No neurological alterations were detected.

Finally, the patient recognized self-induced suicidal ideation with drug overdose. After being evaluated by psychiatry and being clinically and analytically stable, and after progressive improvement of the multiorgan failure after 14 days of admission to the ICU, he was transferred to the hospital floor and presented complete recovery when discharged home.

Discussion

Few cases of intoxication by this drug have been described in the literature, it is however known that it has a narrow therapeutic margin. Ingestion levels above 0.5 mg/kg result in serious clinical cases, and it is almost always lethal above 0.8 mg/kg [4]. Therefore, it is essential to inform the patient of the dose to be taken and of the possible adverse effects if this dose is exceeded, bearing in mind the possibility of self-medication, accidental ingestion, or autolytic attempt.

Colchicine is rapidly absorbed through the digestive tract, reaching the maximum plasma peak between 50 min and 2 hours. Its binding to plasma proteins is weak and its elimination begins in a range of approximately 2 to 20 hours. It is eliminated mainly by the hepatic route in 80% (demethylation by isoenzyme A4 of cytochrome Y450) and by the renal route in 20% (without modification), so its clearance will depend on the proper functioning of these organs [2].

Three phases have been observed in cases of intoxication [4,5]:

Phase I (0-24 hours): the first hours may be asymptomatic or nonspecific, although gastrointestinal symptoms have been reported to predominate 4-6 hours after ingestion [6], given the large enterohepatic circulation of the drug and the high cellular turnover of the intestinal mucosa. Arterial hypotension may be due to smooth muscle toxicity. Fluid extravasation leads to dehydration and hydroelectrolytic alterations.

Phase II (1-7 days): bone marrow suppression, producing leukopenia and thrombopenia, with risk of infectious complications and hemorrhage. In parallel, there is direct toxicity in the myocardium, which may cause arrhythmias.

Acute respiratory failure may develop in the context of capillary damage and extravasation, producing acute pulmonary edema.

Renal failure and rhabdomyolysis with subsequent myoglobinuria may occur, as well as hematuria and proteinuria.

Neurologically, it may present deterioration of the level of consciousness up to coma, as well as convulsions, and at the peripheral level there may appear axonal neuropathy with diminution or loss of osteotendinous reflexes.

Phase III (>7 days): medullary reactivation with leukocytosis. Alopecia is frequently observed, given the antimitotic effect of colchicine on hair follicles (anagen defluvium).

Regarding therapeutic measures, early identification of the different associated organ failures and offering the appropriate organ support treatment is crucial [7]. Initial measures are gastric lavage (useful within the first two hours), administration of activated charcoal (decreases absorption and enterohepatic circulation) and fluid resuscitation aimed at

preventing renal failure which usually appears in the context of hypovolemia due to capillary leakage and myotoxicity (rhabdomyolysis). It is not indicated to undertake extrarenal depuration therapy with the intention of eliminating the drug, since, due to its high volume of distribution, liposolubility and high binding to plasma proteins, it is not dialyzable [8]. However, support with extrarenal clearance should be offered if otherwise indicated [9].

There is a specific antidote, which is a monoclonal Fab antibody with high affinity for colchicine, but it is still under study and is not yet available on the market. It redistributes the drug from the tissues to the plasma, increasing the total concentration of colchicine in blood, but decreasing the free concentration of colchicine, which is the one that exerts the toxicity. It could reverse hemodynamic alterations but does not prevent hematologic toxicity if administration is delayed [5,8].

In the context of multiple organ failure, it is essential to initiate life support measures in the intensive care unit. Vasoactive support should be initiated, hydroelectrolytic alterations should be corrected, and extra-renal depuration therapy or ventilatory support should be considered, if necessary [7]. Urine alkalinization may be indicated in the presence of rhabdomyolysis.

Regarding bone marrow suppression, the benefit of transfusion support and treatment with granulocyte colony stimulators has also been reported [10], and broad-spectrum antibiotic coverage should be empirically considered until microbiological isolation.

In the reported case, most of the toxic side effects of colchicine were observed following the described temporal sequence: gastrointestinal symptoms (diarrhea and vomiting), arterial hypotension, pancytopenia, myocardial damage with CK elevation, respiratory failure, renal failure, alopecia, etc. Despite this and subsequent infectious complications, with early and adequate supportive treatment of his successive organ failures, the patient survived and made a full recovery.

Conclusion

Colchicine is a widely used drug with possible serious adverse effects if the recommended dose is exceeded. Survival in colchicine intoxication at such high doses is very rare and is usually related to autolytic ideation processes.

In routine clinical practice there is no antidote or specific treatment available to improve the prognosis of these patients, hence the measures are always aimed at correct monitoring and providing organic support measures in the intensive care unit if necessary.

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