CASE REPORT

Severe colchicine intoxication; always lethal?!?

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Abstract

Colchicine is a frequently used drug in the treatment and prevention of acute gout. It has a narrow therapeutic index. Lethal intoxication has been reported after ingestion of 7 mg. Colchicine has a large volume of distribution and binds to intracellular tubulin. This causes a disturbance at the cellular level in all tissues with disruption of the microtubular network, leading to multi-organ dysfunction and even failure.

In this case report we describe a 19-year-old patient who visited the emergency room 20 hours after a suicide attempt by ingestion of an estimated 35 mg of colchicine. Because of haemodynamic instability and multi-organ failure, she was admitted to the intensive care unit. The patient survived and was discharged 19 days after admission.

Introduction

Colchicine is a drug frequently used in the treatment and prevention of gout.[1] It has a narrow therapeutic index, with no clear-cut distinction between nontoxic, toxic and lethal doses.[2] Ingestion of more than 0.5 mg of colchicine per kilogram bodyweight causes serious side effects and can even be fatal.[3] Lethal intoxications have been reported after ingestion of only 7 mg of colchicine.[2,4] In this case report we describe a 19-year-old patient who survived an auto-intoxication with 35 mg of colchicine. In the Dutch medical literature, survival after ingestion of such an amount of colchicine has never been described.

Case description

A 19-year-old woman with an unremarkable medical history came to the emergency room, 20 hours after a suicide attempt by ingestion of an estimated 35 mg of colchicine (0.64 mg per kilogram bodyweight) because of symptoms of abdominal pain, vomiting since ingestion and persistent drowsiness. Previously, she was a healthy young woman, who did not use any medication or alcohol.

On admission, the patient presented with a Glasgow Coma Scale of 14. Her blood pressure was 76/51 mmHg, pulse rate 112 /minute in sinus rhythm, and respiratory rate 28 breaths/minute with oxygen saturation 95% while breathing 12 litres of O_2. The patient had a core temperature of 38.1 °C. Painful palpitation of the abdomen, in the epigastric region, was the only finding during physical examination.

Laboratory results (*table 1*) revealed a leucocytosis of 63/nl (reference range 4.0-10.0/nl), impaired liver function tests with an alanine transaminase of 47 U/l (< 35 U/l), aspartate transaminase of 340 U/l (< 30 U/l), alkaline phosphatase of 549 IU/l (40-120 IU/l), gamma-glutamyl transpeptidase of 60 U/l (< 40 U/l) and a lactate dehydrogenase of > 2500 U/l (< 250 U/l). In addition, the patient had acute kidney injury with a creatinine of 239 µmol/l (50-100 µmol/l) and a potassium of 5.5 mmol/l (3.5-5.0 mmol/l). The glucose was 4.8 mmol/l, the international normalised ratio (INR) 6.0. Arterial blood gas analysis showed a pH of 7.26 with a lactate of 9.5 mmol/l (< 1.3 mmol/l).

The patient was admitted to the intensive care unit because of haemodynamic instability with signs of multi-organ failure. Supportive treatment, including volume resuscitation and administration of norepinephrine, was started. Multiple doses of activated charcoal were given. Because of an impaired coagulation state caused by liver failure, and later also thrombocytopenia, we decided to strive for complete correction with procoagulant therapy (pro-thrombin complex concentrate, protamine and fibrinogen concentrate). The abdominal pain was treated symptomatically with a proton pump inhibitor, morphine and butylscopolamine. In addition antibiotic prophylaxis with cefotaxime and metronidazole was started to prevent infection due to bacterial translocation. Furthermore the patient was treated for 24 hours with N-acetylcysteine according to the hospital protocol for acetaminophen overdose.

Table 1. Laboratory results.

Laboratory results	Reference values	At presentation	Day 2	Day 3	Day 7
Haemoglobin mmol/l	7.5-10.0	10.2	7.5	5.9	5.6
Platelet count /nl	150-400	220	47	10	50
WBC /nl	4.0-10.0	63	23.9	1.8	31.4
Aspartate transaminase U/l	< 31	340	400	270	46
Alanine transaminase U/l	< 34	47	55	100	53
Lactate dehydrogenase U/l	< 247	> 2500	> 2500	> 2500	1171
Creatine kinase U/l	< 145	383	1172	1391	457
Alkaline phosphatase IU/l	40-120	549	348	46	82
Gamma-glutamyl transpeptidase U/l	< 38	60	37	40	32
Urea mmol/l	2.5-6.4	10	13	8.7	13
Creatinine µmol/l	50-100	239	130	88	77
C-reactive protein mg/l	< 6	90	150	120	44
APTT sec	30.0-41.0	109.8	64.5	41	
Prothrombin time sec	12.0-14.5	54.4	32.7		
Fibrinogen g/l	2.0-4.0	< 0.30	0.55		
D-dimer mg/l	< 0.5	> 4			
INR (PT)		7.6	3.6	1.6	

This table shows the laboratory results of the first seven days of admission. The patient initially developed leukocytosis. On day 2 of admission, bone marrow depression occurred with a sharp decline in the WBC. In addition, the patient had impaired liver function tests and an acute kidney injury. WBC = white blood cell; APTT = activated partial thromboplastin time; INR = international normalised ratio.

During the first day after admission, laboratory results (*table 1*) revealed a progressive leucocytosis. On the second day, bone marrow depression occurred. Therefore the patient was treated with granulocyte colony-stimulating factor (GCS-F) and thrombocyte concentrate transfusion. There was progressive liver failure manifesting in a spontaneously elevated INR and impaired gluconeogenesis with hypoglycaemia. Because the patient developed an ileus with deferred defecation and gastric retention, total parenteral nutrition was started. Renal function improved spontaneously.

After four days, the patient developed respiratory insufficiency due to acute respiratory distress syndrome (ARDS) and was intubated. At the ninth day, the patient developed fever up to 41 °C. We attributed this to a combination of the intoxication with colchicine, a possible bacterial translocation in the abdomen and a central venous catheter infection. The catheter was removed and the patient was treated with vancomycin.

Eleven days after admission, the patient developed alopecia. At the 14th day, the patient was extubated and after 19 days finally discharged in a clinically good condition, after psychiatric assessment.

Discussion

In the Netherlands, colchicine is registered for the treatment of acute gout.[1] It is also used to treat familial Mediterranean fever, Behçet disease, sarcoidosis, psoriasis, sclerodermia and amyloidosis.[2,3] Colchicine is a neutral lipophilic alkaloid with mild anti-inflammatory activity,[3] and strong anti-mitotic activity.[2]

Colchicine is rapidly absorbed from the gastrointestinal tract and is rapidly distributed to all tissues.[3] In a therapeutic dose, its protein binding is 10-50% and volume of distribution ranges between 2 and 12 l/kg; in overdose it reaches up to 21 l/kg.[3] Colchicine binds to the intracellular protein tubulin, which causes disruption of the microtubular network and results in impaired protein assembly in the Golgi apparatus, decreased endocytosis and exocytosis, altered cell shape, depressed cellular motility, and arrest of mitosis.[3] Because chromosome separation depends on microtubular function, in a toxic dose colchicine arrests mitosis in the metaphase.[3] Tissues with high cell turnover rates (for example: bone marrow, gastrointestinal tract, and hair follicles) are most vulnerable and most readily affected.[3]

Colchicine is eliminated primarily by hepatic metabolism by the CYP 3A4 isoform of cytochrome P450, which involves deacetylation and demethylation, followed by biliary excretion.[3] Colchicine and its metabolites undergo significant enterohepatic re-circulation.[3]

In addition, colchicine has a renal excretion of 10-20%.[4,5]

The characteristic manifestation of acute colchicine toxicity, with three defined but overlapping phases and multi-organ involvement,[3,6,7] is clearly illustrated in our case report. The first stage presents with gastrointestinal mucosal damage; a cholera-like syndrome may develop,[3] with abdominal pain, nausea, vomiting and diarrhoea.[6] In addition, patients are suffering from fever,[5] initial leukocytosis[6] followed by leukopenia[5] and volume depletion.[6]

Stage two develops 24-72 hours post-ingestion and is associated with life-threatening complications,[2,6] characterised by multi-organ dysfunction and metabolic derangements.[3] It may include perturbations of any organ system: bone marrow depression (pancytopenia often developing between 2-5 days after ingestion), haemolytic anaemia, liver damage,[2] gastrointestinal symptoms with ileus and bacterial translocation,[6] renal failure, respiratory distress syndrome, arrhythmias, neuromuscular disturbances, and disseminated intravascular coagulation.[2] If patients survive beyond the second stage, the third stage starts after a week.[6] In this stage, transient alopecia and a rebound leukocytosis are manifest.[2,6]

Generally, treatment of colchicine intoxication is supportive because to date there is no effective antidote.[2] It includes the administration of fluids and antibiotics together with haemodynamic monitoring.[4] In early (i.e. 1-2 hours after ingestion) presentations of large ingestions, efforts to remove any remaining colchicine from the gastrointestinal tract by gastric lavage followed by activated charcoal should always be attempted.[3] Multiple-dose activated charcoal may help prevent entero-hepatic recirculation of the drug.[2] Antibiotics should be given if a secondary infection is suspected.[3] Granulocyte colony-stimulating factor should be considered if leukopenia occurs. It is thought that it accelerates the production of neutrophils within the bone marrow and helps to prevent the development of sepsis.[3] Extracorporeal elimination (e.g. by haemodialysis and haemoperfusion) is ineffective, mainly because of the large volume of distribution.[3,8]

Colchicine-specific Fab fragment antibodies have been used successfully in the treatment of severe colchicine intoxication.[2,9] However, such a treatment modality is not commercially available in the Netherlands.

It is noteworthy that our patient was treated with the N-acetylcysteine protocol for acetaminophen overdose. Iosfina et al. hypothesised that N-acetylcysteine may counteract the inhibiting effects of colchicine on the endogenous antioxidants and may decrease cell death by apoptosis and contribute to survival.[5] Still, the exact underlying mechanism of action remains to be elucidated. However, thorough studies of the effect are not available. Therefore, in our case, the favourable outcome cannot directly be related to this treatment.

This case report made us realise that there is no protocol on www.toxicologie.org for colchicine intoxication. Therefore, we initialised the development of such a protocol.

Conclusion

Colchicine overdose is a life-threatening condition. Colchicine binds to the intracellular protein tubulin causing disturbed mitosis in all tissues followed by multi-organ failure. This case report describes a 19-year-old patient who survived an excessive dose of colchicine, five times the dose which has been described as lethal.

References

1. CVZ. Farmaceutisch kompas: colchicine. www.fk.cvz.nl.
2. Ozdemir R, Bayrakci B, Teksam O. Fatal poisoning in children: Acute Colchicine intoxication and new treatment approaches. Clin Toxicol. 2011;49:739-43.
3. Finkelstein Y, Aks SE, Hutson JR, et al. Colchicine poising: the dark side of an ancient drug. Clin Toxicol. 2010;48:407-14.
4. Caraco Y, Putterman C, Rahamimov R, Ben-Cherit E. Acute Colchicine Intoxication – Possible Role of Erythromycin Administration. J Rheumatol. 1992;19:494-6.
5. Iosfina I, Lan J, Chin C, Werb R, Levin A. Massive Colchicine Overdose with Recovery. Nephrol Urol. 2012;2:20-4.
6. Schut NH, Romijn JA. Multi-orgaanfalen door colchicine-intoxicatie. Ned Tijdschr Geneeskd. 1990;134:1508-10.
7. Usumoto Y, Hifumi T, Kiriu N, et al. Survival case of colchicine intoxication following ingestion of a lethal dose. Chudoku Kenkyu. 2010;23:303-8.
8. Mégarbane, B. Is early implementation of extracorporeal life support in severely colchicine-poisoned patients lifesaving? Definitive evidence is still lacking. Intensive Care Med. 2013;39:1509-10.
9. Baud FJ, Sabouraud A, Vicaut E, et al.: Treatment of Severe Colchicine Overdose with Colchicine-Specific Fab Fragments. New Engl J Med. 1995;332:642-5.