Journal Homepage: -www.journalijar.com

INTERNATIONAL JOURNAL OF ADVANCED RESEARCH (IJAR)

Article DOI:10.21474/IJAR01/15975
DOI URL: http://dx.doi.org/10.21474/IJAR01/15975

*RESEARCH ARTICLE*

# SUICIDAL INGESTION OF MASSIVE COLCHICINE OVERDOSE WITH RECOVERY

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## *Manuscript Info*

***Manuscript History***
Received: 31 October 2022
Final Accepted: 30 November 2022
Published: December 2022

***Key words:-***
Colchicine, Intoxication, Lethal Dose, Multiple Organ Failure, Suicide, Acetyl Cysteine, Overdose

## *Abstract*

Colchicine is an active alkaloid that is commonly used for treatment of multiple diseases including gout, primary biliary cirrhosis and familial Mediterranean fever. Less commonly it has been implicated in several fatal overdoses. Deaths from colchicine overdoses are usually due to multiple organ failure, whether directly from colchicine toxicity or due to ensuing sepsis. We report an extreme case of colchicine ingestion (200 tablets, 0.5 mg ,1.6mg/kg) which is the largest reported non fatal colchicine overdose.Early implementation of a targeted therapeutic plan directed at the predicted multi organ failure which included aggressive use of activated charcoal, timely supportive measures including broad spectrum antibiotics and G-CSF for sepsis, ventilatory support, renal replacement therapy as well as as transfusion of blood and blood products resulted in complete recovery and discharge of the of patient off dialysis.



## Introduction:-

Colchicine is used for the treatment of gout, familial mediterranean fever, amyloidosis and primary biliary cirrhosis. Despite its merits, its narrow therapeutic index has resulted in several fatalities by suicidal overdose. Deaths from colchicine overdose are uncommon but well dowmented and are associated with high mortality rate. We present here a case of profound overdose, potentially the largest consumption reported in the literature from which patient successfully recovered. A multifaceted, aggressive set of interventions instituted early and preemptively may well have been the reason for successful outcome for this patient. Appreciating the mechanism of action by which colchicine causes cell damage and instituting supportive therapies important learning from this case.

**Case presentation**

A 16 year old male presented to accident and emergency department of our hospital with 4 hours history of generalized pain abdomen, vomiting and watery diarrhea. He was a known case of familial Mediterranean fever. Initially patient was thought to have relapse of familial Mediterranean fever and he was admitted. Initially, neither the patient nor the family reveal about ingestion of colchicine. Over the next few hours, patient developed intractable vomitting, severe abdominal pain and profuse diarrhea. At this point patient family revealed that the patient has ingested two bottles of tablet colchicine each containing 100 tablets of 0.5mg.Appreciating the future outcomes of such large dose of intoxication patientt was shifted to intensive care unit for further management. He was started on broad spectrum antibiotics, infusion Omeprazole, N-acetyl cysteine, IV fluids and activated charcoal. His initial vital signs at presentation were : BP 116/67 mmHg, HR 133 bpm, T 37 $^{o}$C. Clinicalexaminationonrevealed a very anxious young boy in distress with generalized abdominal tenderness and distention. Plain x-rays of abdomen showed dilated bowl loops. Patient was seen by surgical team who advised to

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continue with conservative treatment. Over the next 4 days while in ICU patient developed severe pancytopenia, became febrile with bilateral pleural effusions and bilateral sung consolidation, generalized petechial rash and ecchymoses. He became severely hypotensive, started desaturating and was started on multiple inotropic supports, was intubated and started on ventilatory support. CT scan Chest showed bilateral pleural effusions and large patch of consolidation in right lower lobe. Considering marked leucopenia patient was started on G-CSF. To block the entero-hepatic circulation of colchicine activated charcoal was continued. His liver and renal functionscontinued to deteriorate and he became anuric. He was started on daily hemodialysis with transfusion of packed red cells and platelets. On 6th day of admission patients all body hair fell. From 9th day of admission onwards he started improvingclinically, became afebrile,leucocyte and platelet counts started improving, urine output started, pleural effusions resolved and opacities of CXR started resolving. His liver functions and renal functions returned to normal and was taken off hemodialysis. On 11th day of admission patient was extubated. He was discharge from hospital on 15th day of admissionn after Psychiatric consultation and was scheduled follow up.

**Table 1:-**

| Laboratory results | Reference values | At presentation | Day 2 | Day 3 | Day 7 |
|---|---|---|---|---|---|
| Haemoglobin mmol/l | 12.0-16.0 | 16.2 | 12.5 | 5.9 | 3.6 |
| Platelet count /nl | 150-350 | 257 | 47 | 10 | 50 |
| WBC /nl | 4.0-10.0 | 16.4 | 23.9 | 1.8 | 31.4 |
| Aspartate transaminase U/l | < 31 | 340 | 400 | 656 | 235 |
| Alanine transaminase U/l | < 34 | 257 | 398 | 544 | 244 |
| Lactate dehydrogenase U/l | < 247 | 1455 | 2400 | > 2600 | 1171 |
| Creatine kinase U/l | < 145 | 383 | 1172 | 1391 | 457 |
| Alkaline phosphatase lU/l | 40-120 | 549 | 348 | 46 | 82 |
| Gamma-glutamyl transpeptidase U/l | < 38 | 133 | 345 | 256 | 116 |
| Urea mmol/l | 2.5-6.4 | 10 | 18.5 | 25.7 | 18 |
| Creatinine gmol/l | 50-100 | 239 | 456 | 489 | 344 |
| C-reactive protein mg/l | < 6 | 90 | 150 | 120 | 44 |
| | | | | | |
| APTT sec | 30.0-41.0 | 111.8 | 54.5 | 41 | |
| Prothrombin time sec | 12.0-14.5 | 44.4 | 36.7 | | |
| 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.

## Discussion:-

Colchicine is a naturally occurring alkaloid with weak anti-inflammatory activity derived from the autumn crocus Colchicum automnale and the glory lily Gloriosa superba.It has been used extensively in the treatment of gout for many centuries and also been recommended in preventing attacks of familial Mediterranean fever and in the treatment of primary biliary cirrhosis, [2] amyloidosis, [3] and condyloma acuminate Colchicine has potent anti-mitotic activity, which is caused by it's binding, both reversibly and selectively, to tubulin, the159953 microtubular protein that disrupts the function of the mitotic spindles in those cells capable of dividing and migrating. Although colchicine is taken up equally by all cells it is thought that those which have the highest cell turnover (that is, the greatest mitotic activity) are most affected.Colchicine is rapidly absorbed from the gastrointestinaltract after ingestion. It undergoes significant first pass hepaticcmetabolism, which primarily involves deacetylation. Subsequent to this, the metabolites undergo widespread entero-hepatic recirculation before being excreted in bile and faeces.It is thought that the extended time period during which thegastrointestinal mucosal cells are exposed to colchicine mayexplain the prominence of the gastrointestinal symptoms oftoxicity. Renal clearance also accounts for

10%–20% of colchicine removal and if normal renal function exists largerfractions can be excreted via this route if a toxic amount hasbeen ingested. Increased urinary excretion also occurs in thepresence of hepatic disease, as there is a reduction in thecapacity for deacetylation. However, if renal and hepaticdiseases coexist the possibility of toxicity greatly increases..[5–8]Overdose with colchicine is uncommon and it exhibits a low therapeutic index althoughthere is great variation in the dose required for significantmorbidity. Patients have survived ingestion of more than 60mg[9]but conversely others have died after ingesting only [7] mgover a prolonged period.[10]There does not seem to be any clearcut separation between non-toxic, toxic or lethal doses of colchicine. Indeed, symptoms of gastrointestinal toxicity such asnausea, vomiting, diarrhoea and abdominal pain are seen in80% of patients on full therapeutic doses and are used as theclinical endpoint in dose titration. Overdose with colchicine constitutes a toxicological emergency and rapid intervention is required. The symptoms oftoxicity are well described in the literature and can beseparated into three characteristic phases (table 2).The large volume of distribution of colchicine and the factthat 50% of its plasma concentration is linked to proteins meansthat methods of extracorporeal removal are ineffective. Therefore, haemodialysis, although of benefit in the treatment of anyassociated renal failure, is not used to increase elimination.[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.6In addition, patients are suffering from fever,[5]initial leukocytosis6followed by leukopenia5and 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]gastroin-testinal 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 our hospital. 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.

**Table 1:-** Phases of colchicine toxicity.

| Phase | Symptoms |
|---|---|
| I 0-24 hours | Nausea, vomiting, diarrhoea, abdominal pain, and anorexia<br>Electrolyte imbalance and hypovolaemia Peripheral leucocytosis |

| | |
|---|---|
| II 2-7 days | Bone marrow hypoplasia, profound leucopenia, and thrombocytopenia<br>Cardiac arrythmias and cardiovascular collapse Respiratory distress, hypoxia, pulmonary oedema, and ARDS<br>Oliguric renal failure<br>Rhabdomyolysis<br>Electrolyte derangements<br>Metabolic acidosis<br>Mental state changes<br>Seizures<br>Peripheral neuropathy and ascending paralysis |
| III 7th day onwards | Rebound leucocytosis<br>Transient alopecia |

## Conclusion:-

Colchicine intoxication is associated with high mortality rate due to multiorgan failure. It is important to inform patients about its potential lethality and givethem an understandable explanation of side effects. A careful watch must be arranged for patients, which can be obtained by close visiting intervals and prescribing limited number of tablets until the next visit, in order to avoid accidental or intentional overdose.

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