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Colchicine

Updated: October 26, 2017.

OVERVIEW

Introduction

Colchicine is a plant alkaloid that is widely used for treatment of gout. Colchicine has not been associated with acute liver injury or liver test abnormalities except with serious overdoses.

Background

Colchicine (kol' chi seen) is an ancient medication that has been used for the treatment of gout for centuries. Colchicine is a plant alkaloid derived from several members of the lily family, including meadow saffron or autumn crocus (originally found in the district of Colchis and called colchicum). Colchicine inhibits microtubule and spindle formation and is believed to act by interference with leukocyte migration to the site of uric acid crystal formation, thereby reducing production of inflammatory mediators. Colchicine does not lower serum and tissue uric acid levels, but is effective in relieving the pain and swelling of acute gout. Colchicine was officially approved for use in the United States in 1961 and it is still widely used with several million prescriptions filled yearly. Current indications include therapy of acute attacks of gout and as maintenance therapy in combination with other agents to prevent attacks. Colchicine is available in multiple generic forms in tablets of 0.5 and 0.6 mg, as well as in fixed combinations with probenecid. The usual adult dose of colchicine is one tablet daily or every other day. Parenteral preparations for intravenous use are also available. Colchicine is also used for familial Mediterranean fever and prevention of amyloidosis. Colchicine has a narrow therapeutic window and side effects are common, particularly with high doses. Common complaints include gastrointestinal upset, diarrhea, nausea, vomiting and hypersensitivity reactions. Overdosage can be fatal.

Hepatotoxicity

Chronic therapy with colchicine is uncommonly associated with serum aminotransferase or alkaline phosphatase elevations and has, indeed, been used off label as therapy of liver diseases, including alcoholic hepatitis and primary biliary cirrhosis. Despite decades of wide spread use, there have been no published cases of idiosyncratic liver disease attributed to colchicine use. Interestingly, liver biopsies done in patients receiving colchicine often show scattered mitotic figures in hepatocytes (ring mitoses) without accompanying liver cell injury.

In high doses, however, colchicine is associated with severe toxicity which can involve the liver. Intentional as well as accidental overdoses of colchicine can be severe and even fatal, usually presenting with vomiting, diarrhea, weakness and metabolic acidosis followed by rhadbomyolysis, shock, sepsis, coma and multiorgan failure. Liver test abnormalities can occur but may be due to rhabdomyosis rather than liver injury. Acute liver failure may arise later, perhaps as a result of shock and multiorgan failure. Colchicine overdose is rarely

associated with frank jaundice or with a hepatitis-like presentation. The liver abnormalities are probably secondary to ischemic injury to the liver or sepsis.

Likelihood score: E (unlikely cause of clinically apparent liver injury).

Mechanism of Injury

The mechanism of colchicine hepatotoxicity is believed to be inhibition of microtubule or spindle formation and mitotic arrest. Indeed, colchicine is used in the laboratory to inhibit microtubular function and for mitotic chromosomal preparations. Colchicine undergoes extensive hepatic metabolism and hepatic adverse events might be more common without the safety valve of gastrointestinal side effects. Colchicines hepatic safety is probably due to the low daily dose taken (less than 1 mg daily).

Outcome and Management

Cases of acute liver injury attributed to colchicine overdose have been self-limited, and the other toxicities of this agent generally overshadowed the hepatic injury. No convincing instances of acute liver failure, vanishing bile duct syndrome or chronic liver injury due to colchicine have been reported.

Drug Class: Antigout Agents

PRODUCT INFORMATION

REPRESENTATIVE TRADE NAMES

Colchicine – Generic, Colcrys®

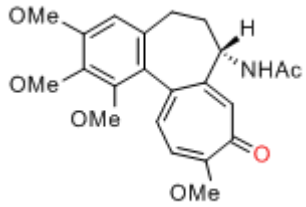
DRUG CLASS

Antigout Agents/Gout Suppressants

COMPLETE LABELING

Product labeling at DailyMed, National Library of Medicine, NIH

CHEMICAL FORMULA AND STRUCTURE

DRUG	CAS REGISTRY NO	MOLECULAR FORMULA	STRUCTURE
Colchicine	64-86-8	C22-H25-N-O6	

ANNOTATED BIBLIOGRAPHY

References updated: 26 October 2017

Zimmerman HJ. Drugs used to treat gout. In, Zimmerman HJ. Hepatotoxicity: the adverse effects of drugs and other chemicals on the liver. 2nd ed. Philadelphia: Lippincott, 1999, pp. 543-4.

(Expert review of hepatotoxicity published in 1999 states that: "despite long-term use of colchicine... , there is little evidence of its causing hepatic injury in humans").

Grosser T, Smyth E, FitzGerald G. Pharmacology of gout. In, Brunton LL, Chabner BA, Knollman BC, eds. Goodman & Gilman's the pharmacological basis of therapeutics. 12th ed. New York: McGraw-Hill, 2011, pp. 994-1004.

(Textbook of pharmacology and therapeutics).

Carr AA. Colchicine toxicity. Arch Intern Med 1965; 115: 29-33. PubMed PMID: 14219498.

(36 year old man given high doses of colchicine [1.2-4 mg daily] developed fever, bone marrow suppression, and sepsis with accompanying rise in alkaline phosphatase [13 to 34 U/L] and AST [to ~90 U/L] without jaundice, ultimately resolving).

Boruchow IB. Bone marrow depression associated with acute colchicine toxicity in the presence of hepatic dysfunction. Cancer 1966; 19: 541-3. PubMed PMID: 5933578.

(69 year old man with obstructive jaundice due to pancreatic cancer developed fatal colchicine toxicity after taking a total dose of 14 mg over 6 days, whereupon he developed fever, bone marrow suppression and hypotension; underlying liver disease may have predisposed to toxicity).

Bruns BJ. Colchicine toxicity. Australas Ann Med 1968; 17: 341-4. PubMed PMID: 5701926.

(14 year old girl took overdose of colchicine [30 mg] and developed abdominal pain, vomiting and diarrhea followed by fever, pancytopenia, confusion, and seizures [bilirubin 1.7 mg/dL, AST 152 U/L, normal Alk P], alopecia appearing during recovery).

Stemmermann GN, Hayashi T. Colchicine intoxication. A reappraisal of its pathology based on a study of three fatal cases. Hum Pathol 1971; 2: 321-32. PubMed PMID: 5095674.

(Three cases of unintentional overdose of colchicine accompanied by vomiting, diarrhea, abdominal pain and followed by metabolic acidosis, renal and bone marrow failure, hypotension, stupor, widespread bleeding and death; liver abnormalities and hepatic necrosis on autopsy were frequent; etiology appears to be arrest of mitoses causing gastrointestinal and bone marrow failure).

Ellwood MG, Robb GH. Self-poisoning with colchicine. Postgrad Med J 1971; 47: 129-38. PubMed PMID: 5576148.

(Two women, ages 16 and 35 years, with intentional colchicine overdose developed nausea, vomiting, dehydration and hypotension followed by alopecia several weeks later; fatal case had centrolobular hepatic necrosis and fat).

Domnguez de Villota E, Galdos P, Mosquera JM, Tomas MI. Colchicine overdose: an unusual origin of multiorgan failure. Crit Care Med 1979; 7: 278-9. PubMed PMID: 446061.

(50 year old man took an overdose [30 mg] of colchicine and rapidly developed fever, diarrhea, vomiting, dehydration and hypotension with renal failure, acidosis, septicemia, and liver test abnormalities [bilirubin 0.7 rising to 6.6 mg/dL, AST 58 to 333 U/L, Alk P 91 to 667 U/L], but ultimate full recovery; sepsis and hypotension may have contributed to the liver abnormalities).

Murray SS, Kramlinger KG, McMichan JC, Mohr DN. Acute toxicity after excessive ingestion of colchicine. Mayo Clin Proc 1983; 58: 528-32. PubMed PMID: 6876886.

(15 year old girl took 2.4 mg of colchicine and rapidly developed nausea, weakness, hypotension, acidosis, respiratory failure and bone marrow suppression [no mention of bilirubin, AST 481 U/L, Alk P 595 U/L], ultimate recovery, alopecia on day 12).

Rosalki SB, Foo AY. Alkaline phosphatase of possible renal origin identified in plasma after colchicine overdose. Clin Chem 1989; 35: 702-3. PubMed PMID: 2702760.

(27 year old woman with colchicine overdose developed rising Alk P [135 rising to 639 U/L], which on analysis was identified as renal in origin).

Baldwin LR, Talbert RL, Sampler R. Accidental overdose of insufflated colchicine. Drug Saf 1990; 5: 305-12. PubMed PMID: 2375835.

(29 year old man and girlfriend snorted colchicine mistaking it for methamphetamine and developed nausea, diarrhea, fever, bone marrow suppression, renal failure and mild enzyme elevations [AST 311 U/L, Alk P 460 U/L], rapidly resolving in patient; the girl friend died).

Putterman C, Ben-Chetrit E, Caraco Y, Levy M. Colchicine intoxication: clinical pharmacology, risk factors, features, and management. Semin Arthritis Rheum 1991; 21: 143-55. PubMed PMID: 1788551.

(Overview of history, chemistry, pharmacokinetics, and side effects of colchicine focusing on features and management of overdose; mentions that liver damage from colchicine is uncommon, but has been described).

Ben-Chetrit E, Levy M. Colchicine: 1998 Update. Semin Arthrit Rheum 1998; 28: 48-59. PubMed PMID: 9726336.

(Review of history, structure, pharmacology, efficacy, side effects and indications of colchicine; overdose can cause cholera-like syndrome of diarrhea, dehydration and shock with renal, cardiac, hepatic, and bone marrow failure).

Brvar M, Kozelj G, Mozina M, Bunc M. Acute poisoning with autumn crocus(Colchicum autumnale L.). Wien Klin Wochenschr 2004; 116: 205-8. PubMed PMID: 15088997.

(71 year old woman ate autumn crocus and developed nausea, diarrhea followed by anemia with AST and LDH levels rising to 8 times ULN, resolving quickly and followed by alopecia during recovery).

Livio Ndiaye F, Wiesel PH, Goy JJ, Genton A. [Abdominal pain and recurrent cholestatic jaundice] Praxis (Bern 1994) 2004; 93: 1051-4. French. PubMed PMID: 15318531.

(70 year old man with heart and kidney transplants, developed jaundice and abdominal pain 1 month after starting colchicine and allopurinol [bilirubin 14.3 mg/dL, ALT 60 U/L, Alk P 244 U/L], resolving with stopping; then had acute abdominal pain and jaundice after 3 days of high doses of colchicine [total dose 7 mg] with bilirubin 5.6 mg/dL, ALT 20 U/L, Alk P 229 U/L, recovering quickly).

Chalasani N, Fontana RJ, Bonkovsky HL, Watkins PB, Davern T, Serrano J, Yang H, Rochon J; Drug Induced Liver Injury Network (DILIN). Causes, clinical features, and outcomes from a prospective study of drug-induced liver injury in the United States. Gastroenterology 2008; 135: 1924-34. PubMed PMID: 18955056.

(Among 300 cases of drug induced liver disease in the US between 2004 and 2008, more than 100 agents were implicated, but not colchicine).

Kamath A, Mehal W, Jain D. Colchicine-associated ring mitosis in liver biopsy and their clinical implications. J Clin Gastroenterol 2008; 42: 1060-2. PubMed PMID: 18391833.

(54 year old man with chronic hepatitis C taking colchicine [0.6 mg/day] had scattered mitotic figures in hepatocytes, in addition to chronic hepatitis on liver biopsy).

Montiel V, Huberlant V, Vincent MF, Bonbled F, Hantson P. Multiple organ failure after an overdose of less than 0.4 mg/kg of colchicine: role of coingestants and drugs during intensive care management. Clin Toxicol (Phila) 2010; 48: 845-8.

PubMed Citation (33 year old woman developed severe diarrhea and hypotension within 24 hours of taking an overdose of colchicine [20 mg], ibuprofen [8 g], diclofenac [1 g], atorvastatin [100 mg] and furosemide [400 mg] with progressive multiorgan failure [bilirubin 1.0 rising to 17.2 mg/dL, ALT 41 to 4710 U/L, CK 211 to 26,990 U/L] over the next 14 days and death).

Smith MW, Roberts DM, Ritson SM, Day RO. Death and morbidity from supratherapeutic dosing of colchicine. Med J Aust 2011; 194: 612-3. PubMed PMID: 21644880.

(Short descriptions of 3 patients who developed severe nausea, vomiting, diarrhea, and myalgias within a few days of startng high doses of colchicine [2-4 mg daily]; one died of multiorgan failure, the other two recovered rapidly upon stopping, one had "hepatic dysfunction").

Iosfina I, Lan J, Chin C, Werb R, Levin A. Massive colchicine overdose with recovery. Case Rep Nephrol Urol 2012; 2: 20-4. PubMed PMID: 23197951.

(47 year old woman took an overdose of colchicine [90 mg] and presented one hour later with abdominal pain, later developing respiratory, renal, cardiovascular and hepatic failure [AST rising from 29 to 15,111 U/L within 3 days], but ultimately recovered).

Little A, Tung D, Truong C, Lapinsky S, Burry L. Colchicine overdose with coingestion of nonsteroidal antiinflammatory drugs. CJEM 2014; 16: 252-6. PubMed PMID: 24852590.

(39 year old woman took an intentional multidrug overdose [25 mg colchicine, 1.25 g indomethacin, 75 mg zopiclone] and presented with severe nausea, vomiting and abdominal pain followed by shock, multiorgan failure and death 52 hours after the ingestion [ALT peak 1050 U/L, AST 4100 U/L, CPK 5,840 U/L, bilirubin not given]).

Aghabiklooei A, Zamani N, Hassanian-Moghaddam H, Nasouhi S, Mashayekhian M. Acute colchicine overdose: report of three cases. Reumatismo 2014; 65: 307-11. PubMed PMID: 24705036.

(Three cases of colchicine overdose, all presenting rapidly with nausea, abdominal pain and diarrhea, and two then developing metabolic acidosis, renal failure, cardiovascular collapse and death).

Fernández S, Castro P, Nogué S, Nicolás JM. [Refractory shock and severe leukopenia with multisystemic organ failure due to colchicine intentional overdose]. Med Clin (Barc) 2014; 143 (3): 140. Spanish. PubMed PMID: 24378151.

(24 year old man developed nausea and abdominal pain within hours of a colchicine overdose [30 mg], followed by acidosis and rhabdomyolysis [CPK 1128 U/L], bone marrow suppression, sepsis and then renal, cardioascular and pulmonary failure, dying 5 days after the ingestion).

Kilic SC, Alaygut D, Unal E, Koç E, Patiroglu T. Acute colchicine intoxication complicated with extramedullary hematopoiesis due to filgrastim in a child. J Pediatr Hematol Oncol 2014; 36: e460-2. PubMed PMID: 24309614.

(3 year old boy took an overdose of his mother's colchicine and developed nausea, vomiting and diarrhea followed by rhabdomyolysis, acidosis, neutropenia and sepsis, which was treated with recombinant G-CSF and was followed by leukocytosis and hepatomegaly which the authors attributed to extramedullary hematopoiesis).

Shuttleworth E, Sawyer R, Holland M, Cooksley T. The perils of Grandma's medication: colchicine toxicity causing pneumomediastinum. Acute Med 2014; 13: 171-3. (19 year old man took an overdose of colchicine [50 mg] and developed refractory vomiting followed by subcutaneous and mediastinum emphysema, bone marrow suppression [white count 1100/μ PubMed PMID: 25521087.

L, platelets 4000/μL], and coagulopathy [prothrombin time 17.9 sec], but recovered with supportive therapy only).

Boonstra JJ, Kan AA, de Vries I, Deneer VH, Meinders AJ. [A potentially fatal intoxication with colchicine]. Ned Tijdschr Geneeskd 2015; 159: A8144. Dutch. PubMed PMID: 25804106.

(18 year old woman took an overdose of colchicine [30 mg] and developed abdominal pain and vomiting followed by anema, thrombocytopenia and paralytic ileus requiring intensive care, but with ultimate recovery; no liver test results provided).

Chalasani N, Bonkovsky HL, Fontana R, Lee W, Stolz A, Talwalkar J, Reddy KR, et al.; United States Drug Induced Liver Injury Network. Features and outcomes of 899 patients with drug-induced liver injury: The DILIN Prospective Study. Gastroenterology 2015; 148: 1340-52.e7. PubMed PMID: 25754159.

(Among 899 cases of drug induced liver injury enrolled in a US prospective study between 2004 and 2013, none were attributed to colchicine).

Arslan MN, Özgün A, Daş T, Kumru D, Şam B, Koç S. Colchicine-induced rhabdomyolysis: An Autopsy Case. Am J Forensic Med Pathol 2016; 37: 57-9. PubMed PMID: 27049658.

(18 year old woman with familial Mediterranean fever developed fatal rhabdomyolysis and shock after a colchicine overdose (4.5 mg), and had moderate fatty liver at autopsy).

Alaygut D, Kilic SC, Kaya A, Oflaz MB, Bolat F, Cevit Ö, Icagasioglu FD. Assessment of 17 pediatric cases With colchicine poisoning in a 2-year period. Pediatr Emerg Care 2016; 32: 168-72. PubMed PMID: 26928096.

(Over a 2 year period, 17 children, ages 1 to 17 years, were admitted to a Turkish referral center for colchicine overdose, 6 had Familial Mediterranean fever and the others had swallowed family members' drug, 8 were symptomatic with nausea, abdominal pain or diarrhea, serum enyzme elevations arose in 2 patients, but were likely due to rhabdomyolysis [peak ALT 119 and 646 U/L, AST 3357 and 3003, CPK 3700 and 75,643 U/L]; all survived).

Lloyd G. Colchicine in overdose. Br J Gen Pract 2016; 66: 605. PubMed PMID: 27884896.

(The author reminds readers: "Please be aware of the devasting consequences of a significant colchicine overdose").

Roddy E, Mallen CD. Colchicine in overdose. Br J Gen Pract. 2017; 67: 61. PubMed PMID: 28126860.

(In answer to Lloyd [2016] "We urge prescribers not to abandon an effective treatment for this excruciatingly painful...condition").