COLCHICINE AND PODOPHYLLIN,

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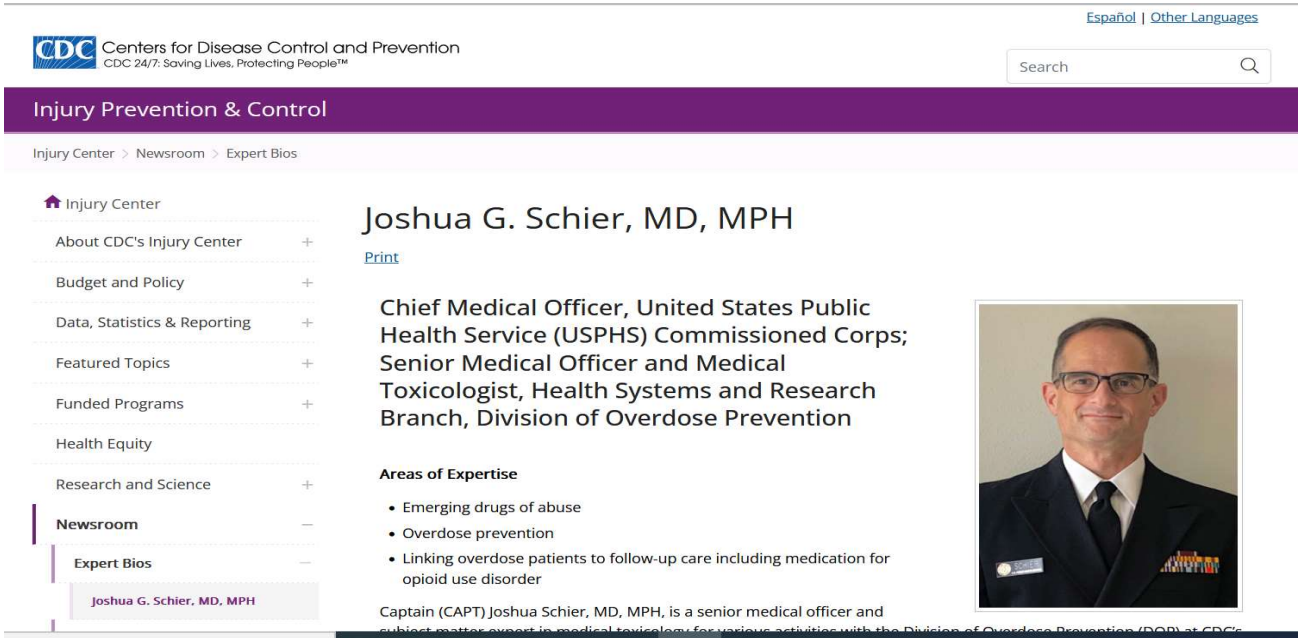


COLCHICINE

- Colchicine, the active alkaloidal component in colchicum, was isolated in 1820 and rapidly became popular as an antigout medication
- Benjamin Franklin reportedly had gout and is credited with introducing colchicine in the United States.
- It is still used in the acute treatment and prevention of gout and is used in other disorders, including amyloidosis, Behçet's syndrome, familial Medi-terranean fever, pericarditis, arthritis, pulmonary fibrosis, vasculitis, biliary cirrhosis, pseudogout, spondyloarthropathies, calcinosis, and scleroderma.

سورنجان
سورنجان یا **گل حسرت** یا **گل حسرتی**
Colchicum))

دلیل نامگذاری این گل به افسانه ای قدیمی باز میگردد. طبق این افسانه ، گل حسرت (سورنجان) در اواخر اسفندماه رشد میکند ، ولی به دلیل تلخ بودن این گل ، موجوداتی مانند پرندگان و پروانه ها به این گل نزدیک نمیشوند . و این گل در حسرت دیدن آنها پژمرده می شود . سپس در پاییز دوباره به شوق دیدن پرندگان و پروانه ها رشد خواهد کرد ولی بازهم در حسرت دیدار این موجودات زیبا میماند.

Case Reports > Ann Intern Med. 1981 Sep;95(3):391-2. doi: 10.7326/0003-4819-95-3-391_2.

Paraquat poisoning and colchicine treatment

W Vincken, L Huyghens, W Schandevyl, D Verbeelen, L Corne

PMID: 7271105 DOI: 10.7326/0003-4819-95-3-391_2

No abstract available

Similar articles

> Isr J Med Sci. 1989 Feb;25(2):92-4.

Effectiveness of vitamin E and colchicine in amelioration of paraquat lung injuries using an experimental model

E Shahar [1], I Keidar, E Hertzeg, Z Barzilay

Affiliations + expand

PMID: 2703331

Abstract

Article

Effects of Colchicine on Pulmonary Injury Induced by Paraquat

January 2003 · Applied Microscopy 33(4)

Authors:

Joong-Kil Kim

Moo-Ung Chang

Jyung-Sik Kwak

COLCHICINE

Pharmacology

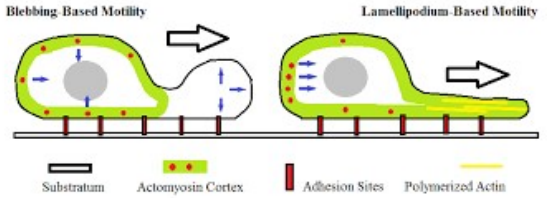
- Colchicine is a **potent inhibitor** of microtubule formation and function → interferes with
    1) cellular mitosis
    2) intracellular transport mechanisms
    3) maintenance of cell structure and shape.

- At doses used clinically, colchicine inhibits **neutrophil and synovial cell** release of chemotactic glycoproteins.

COLCHICINE
Pharmacology

- Colchicine accumulates in **leukocytes** → inhibitory effects on :

1) leukocyte adhesiveness
2) ameboid motility
3) Mobilization
4) lysosome degranulation
5) chemotaxis.



- Colchicine also inhibits microtubule polymerization, which disrupts inflammatory cell-mediated chemotaxis and phagocytosis.
- Colchicine also acts as a competitive antagonist at GABAA receptors.

COLCHICINE
Pharmacokinetics and Toxicokinetics

- Colchicine is rapidly absorbed in the jejunum and ileum
- bioavailability = 25% -50%.
- It is highly lipid soluble
- volume of distribution=2.2 to 12 L/kg, → increase to 21 L/kg in overdose.
- Protein binding = 50%
- During the first several hours after acute overdose, colchicine is sequestered in white and red blood cells (RBCs) in concentrations 5 to 10 times higher than serum.
- T max = between 1 to 3 hours.
- Toxic effects usually do not occur with concentrations < 3 ng/mL.
- Colchicine is primarily metabolized through the liver with up to 20% of the ingested dose excreted unchanged in the urine.

- Enterohepatic recirculation of colchicine occurs.

COLCHICINE
Pharmacokinetics and Toxicokinetics

- the serum colchicine elimination half-lives **= 9 to 108 minutes →** rapid initial distribution phase
- a delayed terminal elimination phase= 1.7 to 30 hours
- ESRD and liver cirrhosis→ elimination h1/2 = 10-fold.

- it is not dialyzable.

COLCHICINE
Drug Interactions

- Colchicine metabolism is susceptible to drug interactions.
- colchicine is detoxified by CYP3A4→ erythromycin, clarithromycin, and grapefruit juice.
- cyclosporine increases colchicine toxicity.
- Co-administration of colchicine with statin or fibrate drugs, cyclosporine, ketoconazole, ritonavir, **verapamil** ER, **diltiazem** ER, fluindione (vitamin K antagonist) → colchicine poisoning.
- colchicine and nephrotoxic xenobiotics (NSAIDs , ACEI) → colchicine poisoning.

COLCHICINE
Toxic Dose

- The toxic dose for colchicine is not well established.
- patients with ingestions > 0.8 mg/kg uniformly died
- those with ingestions > 0.5 mg/kg but < 0.8 mg/kg → survive if given supportive care
- death occurs with doses < 0.5 mg/kg, conversely, some patients survive ingestions reported to be in excess of 0.8 mg/kg.
- many comorbid conditions (eg, **kidney disease**) and other pharmaceuticals, which when coadministered can enhance colchicine's adverse health effects; this complicates the determination of a minimal toxic dose.

COLCHICINE
Clinical Presentation

TABLE 34–1 Colchicine Poisoning: Common Clinical Findings, Timing of Onset, and Treatment

Phase	*Time*[a]	*Signs and Symptoms*	*Therapy or Follow-Up*
I	0–24 h	Nausea, vomiting, diarrhea	Antiemetics
			GI decontamination for early presentation
		Salt and water depletion	IV fluids
		Leukocytosis	Close observation for leukopenia for 24 h
II	1–7 days	Risk of sudden cardiac death (24–48 h)	ICU admission and appropriate resuscitation
		Pancytopenia	G-CSF
		Acute kidney injury	Hemodialysis
		Sepsis	Antibiotics
		ARDS	Oxygen, mechanical ventilation
		Electrolyte imbalances	Repletion as needed
		Rhabdomyolysis	IV fluids, hemodialysis
III	>7 days	Alopecia (sometimes delayed 2–3 wk)	Follow-up within 1–2 mo
		Myopathy, neuropathy, or myoneuropathy	EMG testing, biopsy, and neurologic follow-up as needed

COLCHICINE
Clinical Presentation

- initial peripheral leukocytosis (as high as 30,000/mm3)
- followed by a profound leukopenia < 1,000/mm3.
- Pancytopenia➔ beginning 48 to 72 hours after overdose
- A rebound leukocytosis and recovery of all cell lines occur if the patient survives.

- Development of dysrhythmias , cardiac arrest and Complete AV block

- colchicine has direct toxic effects on skeletal and cardiac muscle, causing rhabdomyolysis

COLCHICINE
Clinical Presentation

- Myopathy neuropathy, and myoneuropathy → long-term therapy and acute poisoning.
- The myoneuropathy is often initially misdiagnosed as polymyositis or uremic neuropathy (caused by coexistent acute or chronic kidney disease).
- Myoneuropathy usually develops in the context of chronic, therapeutic dosing in patients with some **baseline renal impairment,** although it is reported to occur in the presence of normal renal function as well.

- Weakness usually resolves within several weeks of drug discontinuation
- Myopathy has also occurred with concomitant use of hydroxymethylglutaryl–coenzyme A reductase inhibitors (**statins**) in patients with chronic kidney disease.
- Myopathy symptoms typically resolve within 4 to 6 weeks, or in some patients, up to 6 to 8 months.

COLCHICINE
Clinical Presentation

- Alopecia is usually reversible
- Occurs 2 to 3 weeks after poisoning in survivors.
- Dermatologic complications range in → epithelial cell atypia to toxic epidermal necrolysis.

- Neurologic effects, including delirium, stupor, coma, delayed encephalopathy, and seizures, are reported in colchicine poisoning

- Other reported complications of colchicine poisoning include bilateral adrenal hemorrhage, DIC, pancreatitis, and liver dysfunction

COLCHICINE
Tests

- However, effective steady-state serum concentrations for treatment of patients with various illnesses are reported as 0.5 to 3.0 ng/mL

- Concentrations > 3.0 ng/mL are associated with toxicity depending on the clinical situation, and concentrations > 24 ng/mL are definitely associated with poisoning

COLCHICINE
Tests

- Serum concentrations do not correlate well with the amount of xenobiotic ingested in massive oral overdose settings.
- CBC, serum electrolytes, LFT, RFT, CPK , phosphate, Ca , Mg, PT, PTT, U/A , Trop , ABG , lactate, fibrinogen, and fibrin split products

- If cardiotoxicity is present or suspected, serial troponin concentrations (every 6–12 hours) are recommended.
- CBC q12.

COLCHICINE
Management

- mainly supportive
  - ✓ IV fluid replacement
  - ✓ vasopressor use
  - ✓ Hemodialysis (for acute kidney injury, not for toxin removal)
  - ✓ Antibiotics for suspected secondary infection
  - ✓ Colony-stimulating factors
  - ✓ Adjunctive respiratory therapy (endotracheal intubation, positive end-expiratory pressure) as indicated.
  - ✓ Consultation with nephrology and hematology specialists
  - ✓ In severe, refractory poisoning, it is reasonable to attempt options such as intraaortic balloon pump therapy and ECMO.

COLCHICINE
Management

- orogastric lavage → within 1 to 2 hours of potentially life-threatening ingestions,

- A dose of activated charcoal (AC) is recommended after lavage or in its place if lavage is not appropriate or possible.
- Because limited evidence supports that colchicine undergoes some enterohepatic recirculation, administration of a single dose of AC to a patient presenting to a health care facility beyond 2 hours after ingestion is recommended if no contraindications exist.
- Multiple-dose activated charcoal (MDAC) is also recommended in these patients as well for the same reason in that the absorption

- Experimental colchicine-specific antibodies can restore colchicine-affected tubulin activity in animal models of colchicine poisoning and was successfully used in a single human case of severe colchicine

COLCHICINE
Management

- Granulocyte-colony stimulating factor (G-CSF) → patients with colchicine-induced leukopenia and thrombocytopenia.
- Dose of G-CSF, the dosing frequency, and the route of administration were variable in the reported cases
- Administration of G-CSF is recommended if the patient begins to manifest evidence of leukopenia.
- Dosing should be in accordance with the manufacturer's instructions.

COLCHICINE
Management

- Hemodialysis and hemoperfusion are not viable options for patients with colchicine poisoning based on its large volume of distribution, but hemodialysis is required if renal failure is present.
- The use of whole-blood and plasma exchange for patients presenting with lethal-dose colchicine exposures was tried, but evidence of efficacy is lacking, and it is not recommended for routine care.

PODOPHYLLUM RESIN OR ODOPHYLLIN

Pharmacology

- Podophyllin is used as a topical treatment for verruca vulgaris and condyloma acuminatum.
- The active ingredient is believed to be podophyllotoxin.
- The derivatives are : for chemotherapeutics → etoposide and teniopside.

PODOPHYLLUM RESIN OR PODOPHYLLIN

Pharmacokinetics and Toxicokinetics

- Podophyllotoxin is highly lipid soluble and easily crosses cell membranes.
- Peak serum concentrations of 1 to 17 ng/mL were achieved within 1 to 2 hours after topical administration of doses ranging from 0.1 to 1.5 mL (0.5–7.5 mg).
- Patients treated with < 0.05 mL→ no detectable podophyllotoxin in their serum.
- Topical administration of 0.1 mL yielded peak serum concentrations up to 5 ng/mL within 1 to 2 hours and up to 3 ng/mL at 4 hours.
- Topical administration of 1.5 mL yielded peak serum concentrations ranging from 5 to 9 ng/mL within 1 to 2 hours, concentrations of 5 to 7 ng/mL at 4 hours, 3 to 4.5 ng/mL at 8 hours, and 3.5 ng/mL at 12 hours.

PODOPHYLLUM RESIN OR PODOPHYLLIN

Pathophysiology

- suggested mechanisms:

A. inhibition of purine synthesis

B. inhibition of purine incorporation into RNA

C. reduction of cytochrome oxidase and succinoxidase activity

D. inhibition of microtubule structure and function.

- Podophyllotoxin causes its toxicity similar to colchicine → bind to tubulin subunits and interfere with subsequent microtubule structure and function

PODOPHYLLUM RESIN OR PODOPHYLLIN

Toxic Dose

- The minimum toxic dose = is unknown.

PODOPHYLLUM RESIN OR PODOPHYLLIN

Clinical Presentation

- Poisoning is described after A) ingestion, B) topical and C) IV administration of podophyllotoxin
- topical typically caused by improper usage :
  - excessive topical exposure
  - interruption in skin integrity
  - failure to remove the preparation after a short time period

- The onset of toxicity is reported to be delayed as long as 12 hours after ingestion.
- Nausea, vomiting, abdominal pain, and diarrhea usually begin within **several** hours after ingestion.
- Symptoms of poisoning is often delayed for 12 hours or more after topical exposure

PODOPHYLLUM RESIN OR PODOPHYLLIN

Clinical Presentation

- Alterations in CNS and PNS function tend to predominate in podophyllin toxicity.
  - Patients present with confusion, obtundation, or coma.
  - Permanent encephalopathy and cerebral atrophy occurred in some cases.
  - Delirium and both auditory and visual hallucinations
  - paresthesias, lost deep tendon reflexes, and developed a Babinski sign.
  - Cranial nerve involvement, including→ diploplia, nystagmus, dysmetria,dysconjugate gaze,1and facial nerve paralysis,
  - Patients who recover from the initial event are at risk of developing a peripheral sensorimotor axonopathy.
  - Dorsal radiculopathy and autonomic neuropathy
- The reported duration for recovery from podophyllin-induced axonopathy is variable but is likely to take several months.

PODOPHYLLUM RESIN OR PODOPHYLLIN

Clinical Presentation

- Hematologic toxicity : likely antimitotic effects
- similar to colchicine but is not nearly as consistent in its pattern, severity, and frequency.
- An initial leukocytosis → followed by leukopenia, thrombocytopenia, or generalized pancytopenia.

PODOPHYLLUM RESIN OR PODOPHYLLIN

Clinical Presentation

- Other complications of poisoning :
  - Fever
  - ileus
  - elevated LFT
  - hyperbilirubinemia
  - coagulopathy
  - seizures
  - acute kidney injury
  - Teratogenic effects → exposure during pregnancy

PODOPHYLLUM RESIN OR PODOPHYLLIN

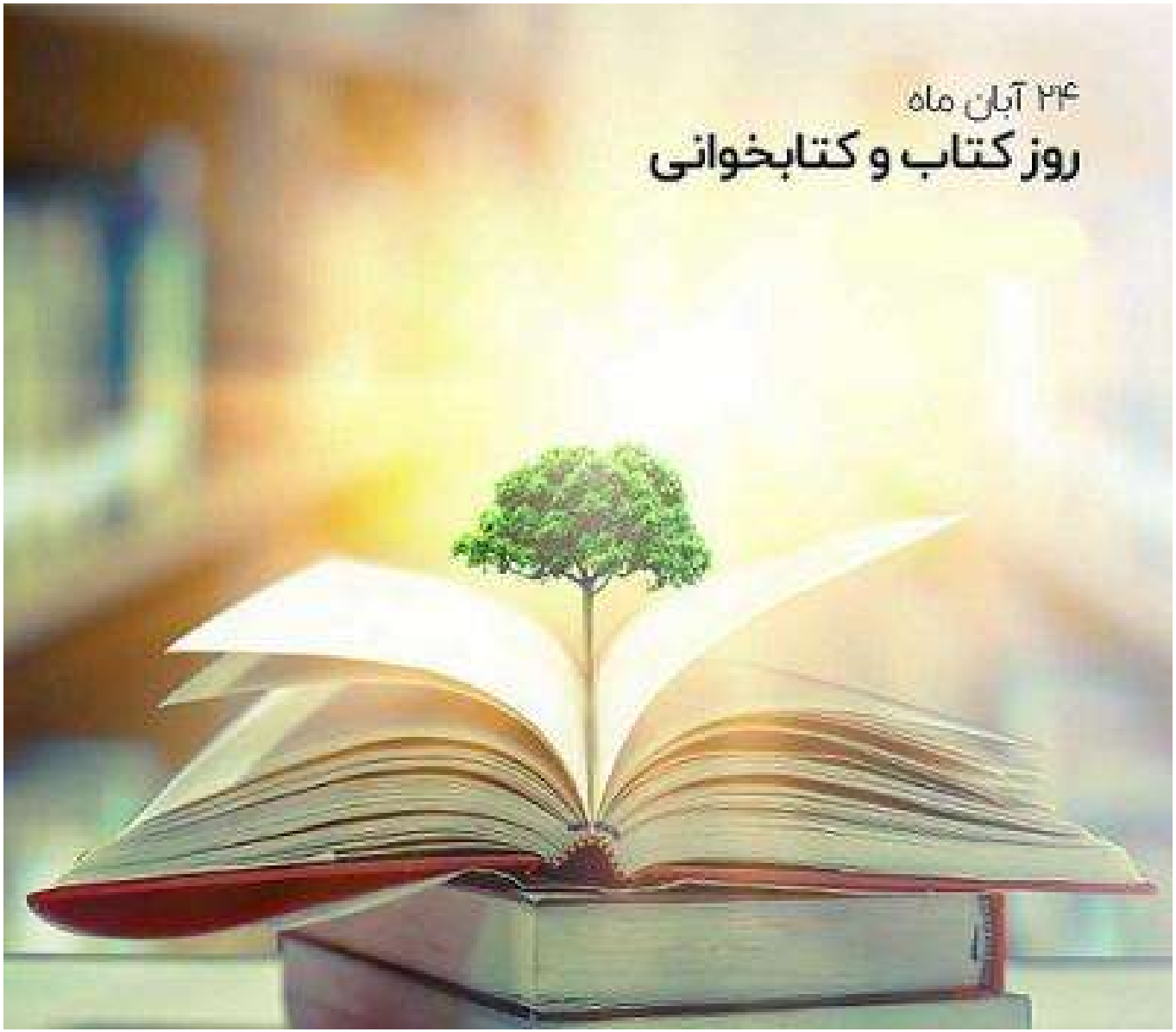
Management

- Management primarily → supportive and symptomatic
- Activated charcoal → within the first several hours of ingestion
- Remove any topically applied podophyllin
- Monitoring Blood cell counts (at least daily).

PODOPHYLLUM RESIN OR PODOPHYLLIN

Management

- A few case reports → resin hemoperfusion and charcoal hemperfusion.→ they cannot be routinely recommended at this time.
- Patients should therefore be observed for the onset of toxicity for at **least 12 hours** after ingestion and at **least 24 hours after dermal** exposures.
- We recommended that asymptomatic patients with unintentional exposures and good follow-up who are discharged after 12 to 24 hours have scheduled follow-up with a primary care physician and a repeat cell blood count within 24 hours.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