Colchicine Poisoning

Diagnosis, management, and public health impact

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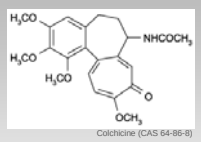
Overview

- Pharmacology of colchicine
- Physiology of microtubules
- Toxicology
- Epidemiology of colchicine poisoning (Europe & U.S.)
- Colchicine poisoning by pharmaceutical colchicine and by plants.
- Clinical presentation
- Prognosis and outcome
- Management

Pharmacology of colchicine

- Colchicine is an alkaloid occuring in the meadow saffron (*Colchicum autumnale*) and in the Glory Lily (*Gloriosa superba*).



Colchicine (CAS 64-86-8)


Colchicum autumnale


Gloriosa superba

Pharmacology of colchicine

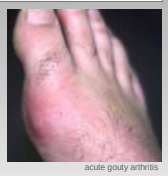
- Indications: Acute gouty arthritis, gout prophylaxis, familial mediterranean fever (familial paroxysmal polyserositis).
  In the past it has been used in primary biliary cirrhosis, psoriasis, Behçet's disease, scleroderma, amyloidosis, and other inflammatory or proliferal diseases.
- Colchicine is a drug with excellent effect in acute attacks of gout: It provides relief within 30-60 minutes.
  But: It has an extremely narrow therapeutic window.

EFFICACY → **TOXICITY**

Goodman & Gilman's 2006
Dollery C. 1991

Pharmacology of colchicine

- **Administration**:
  acutely: max. 6 mg orally or 3 mg i.v.
  chronically: 1.0 to 1.5 mg per day orally
  Today tendency towards lower dosages.
- **Toxicity**: 0.5 mg/kg severe toxicity
  >0.8 mg/kg fatal
- **Safety recommendations**:
  1) Single i.v. dose 2-3 mg (not to be exceeded) maximum 4-5 mg
  2) Interval: No other colchicine for 7 days !
  3) Dose reduction on hepatic or renal failure
  4) Severe hepatic diseases or renal failure (renal clearance < 10 mL/min.) are absolute contraindications.


acute gouty arthritis

Wallace SL, Singer JZ. J Rheumatol 1988, 15: 495-9.
Moreland LW, Ball GV. Arthritis Rheumatism 1991; 34: 782-6.

Pharmacology of colchicine

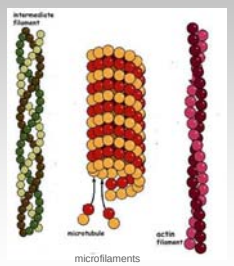
- Absorption: rapid, incomplete? (oral bioavailability 25-50%); peak concentration 0.5 to 2 hours after dosing. Enterohepatic recirculation with biphasic plasma concentration.
- V_d = 2 L/kg; protein binding: 30-50%
  plasma $t_{½}$ = 10 to 60 min. (after intravenous administration)
  elimination halflife = 10 to 60 hours (from leucocytes)
- Concentrated in leucocytes; kidneys, liver, spleen, gut.
- Metabolism: hepatic (CYP3A4), various metabolites;
  Inhibition of CYP3A4 and p-glycoprotein increases toxicity.
- Excretion: 20% unchanged renally, 5-50% biliary.
- Breast milk: + + (corresp. to plasma conc.)
- Crosses the placenta

Goodman & Gilman's 2006; Dollery C. 1991
Rochdi M et al. Hum Exper Toxicol 1992; 11: 510-6
Tröger U et al. BMJ 2005; 331: 613
Guillonneau M et al. Eur J Obstet Gynecol 1995
Milunsky JM et al. J Pediatr 1991
Amoura Z et al. J Rheumatol 1994

Microtubules

Cellular microfilaments

- Cytoskeleton
- 3 forms:
  - actin filaments
  - intermediary filaments
  - microtubules
- functions:
  - mechanical support
  - organelle position
  - directs cell expansion



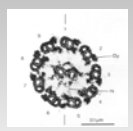
microfilaments

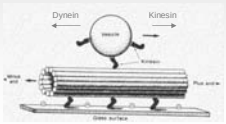
http://www2.mcdaniel.edu

Microtubules

Physiological role of microtubules

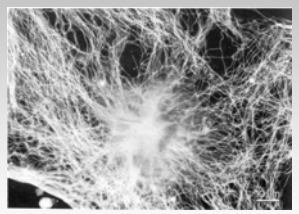
- Cytoskeleton
- Cellular polarity
- Cellular motility
  - organelles
  - proteins
  - ciliae and flagellae
  - cell migration
- Cellular transport
- Phagocytosis
- Mitosis



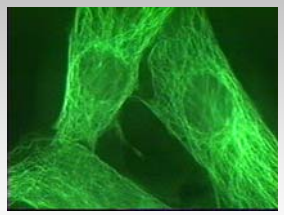


Microtubules

The cytoskeleton



Immunofluorescence staining of microtubules (fibroblast)

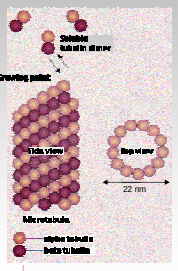


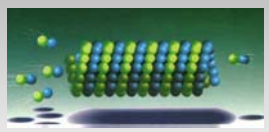
Rat aortic smooth muscle cells stained with anti-tubulin antibody

Dustin P. Microtubules, 1978
http://dept.kent.edu

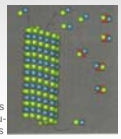
Microtubules

Microtubule formation





Microtubule formation is is extremely dynamic (halflife = 10 min.)



Colchicine blocks assembly of tubuline heterodimers

http://www.cytochemistry.net

Microtubules

Microtubule impairment by colchicine leads to

- blocking of mitosis
- reduction of neutrophil migration
- decreased chemotaxis, adhesion and phagocytosis of leucocytes
- negative inotropic effect
  (decrease in sarcoplasmatic reticulum function and decrease in calcium myofilament sensitivity)
- neurotoxicity (impaired axonal transport and vesicle release)

Conaghan PG, Day RO. Drug Saf 1994
Mery P et al. Intensiv Care Med 1994

Epidemiology

Reasons and circumstances of colchicine poisoning

- intentional ingestion (suicide attempts), using tablets or plants
- confusion with edible plants
  (wild garlic, *A. ursinum; G. superba* tubers)
- therapeutic errors
  - inadequately high doses
  - treatment duration (failure to stop)
- illicit drug adulteration

Gossweiler B. Schweiz Rdschau Med Praxis 1985; 74: 1443-9
Öztekin A. Ann Pharmaceut Fran 1994; 52: 260-5
Nagaratnam N et al. Trop Geogr Med 1973; 25: 15-7
Baldwin LR et al. Drug Saf 1990; 5: 305-12

Epidemiology

Plant ingestion

- occurs rarely but regularly
- fatalities have been reported
- exposure usually is accidental
- confusion of wild garlic with meadow saffron
- 30-85 g leaves may be fatal (0.07-0.2% colchicine)

Colchicum autumnale

Allium ursinum

Borron S et al. Hum Exp Toxicol 1996

Epidemiology

Colchicine poisoning in Europe

- E-mail based survey in all European Poisons Centres listed in the EAPCCT Poisons Centre Directory (80 PCs in 33 countries) in October 2004, reminder in April 2005.
- asking for
  - the number of human cases of colchicine poisoning 1999 to 2003
  - the number of fatal human cases
  - the number of cases due to *C. autumnale* ingestion
- No investigation on individual cases

Kupferschmidt H, Campbell A. Clin Tox 2005; 43: 399

Epidemiology: Europe

Poisons Centres responding	44	55%
with cases	34	77%
without cases	10	23%
average per PC	16	1-79
Countries responding	20	61%
Total cases (5 years)	547	
Fatal cases	32	5.8%
C. autumnale	134	24%
U.K. Toxbase accesses *)	265	
tablets	227	86%
Colchicum	38	14%

*) not known if case-related or general information only

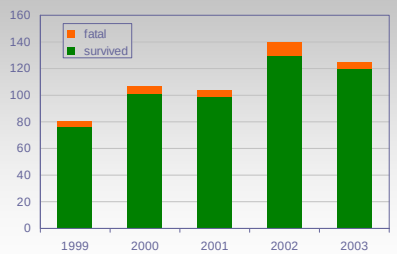
Epidemiology: Europe

Fatalities

- Of the 32 fatal cases, 10 were reportedly due to *Colchicum autumnale* ingestion (31%).

Epidemiology: Europe

Total cases reported per year



Epidemiology: Europe

Colchicine poisoning in Europe: Summary

- Colchicine poisoning occurs in most European countries, sparing only a few of them (Iceland, Finland).
- Approx. 25% of them are due to C. autumnale ingestion.
- Fatality rate 5-6%, higher in plant ingestion.
- If extrapolated to all Poisons Centres (incl. those not having responded), the total number of cases may vary between 100 and 200 per year with an annual number of 6-12 fatal cases

Epidemiology: Europe

Limitations

- Study is only e-mail based.
- Retrospective study design.
- No detailed clinical data available.
- Variation in data retrieval and data recording in the individual countries and Poisons Centres which have participated.
- Extrapolation to entire Europe not reliable.

Epidemiology: U.S.

Colchicine cases in TESS 1999-2005

YEAR	Tablets	Plant	Total
1999	146	24	170
2000	159	21	180
2001	195	25	220
2002	235	12	247
2003	231	11	242
2004	310	22	332
2005	312	8	320
Total	1588	123	1711
Average	226.9	17.6	244.4

TESS Annual Reports

Epidemiology: U.S.

Age groups, reason of exposure, and outcome

Age groups	Total	Average
<6	458	65.4
6-19	155	22.1
>19	1087	155.3

Reason of exposure		
unintentional	1045	166.3
intentional	317	45.6
other	3	0.4
ADR	214	30.9

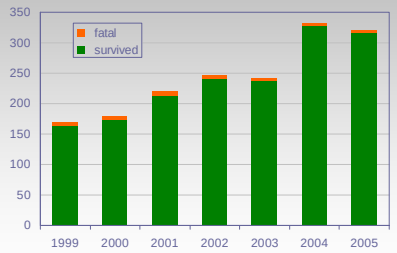
Epidemiology: U.S.

Age groups, reason of exposure, and outcome

Outcome	Total	Average
none	443	63.3
minor	283	40.4
moderate	188	26.9
major	51	7.3
death	37	5.3

Epidemiology: U.S.

Total cases reported per year



Epidemiology: U.S.

Fatalities

- Of the 37 fatalities, none was due to *Colchicum autumnale* ingestion.

	<6 yo	6-19 yo	>19 yo
Tablets	374 (82%)	142 (92%)	1062 (98%)
Plant	84 (18%)	13 (8%)	25 (2%)
TOTAL	458	155	1087

Epidemiology

Comparison Europe - U.S.

- Europe

Population (millions)	580
Cases / million population [1)]	0.26
Fatalities / million population	0.017

[1)] estimate from assumption 150 cases, 10 fatalities

- U.S.

Population served by PCs (mio)	284
Cases / million population	0.86
Fatalities / million population	0.019

http://epp.eurostat.ec.europa.eu
TESS Annual Reports 1999-2005

Clinical presentation

- Phase 1 (24 hours)
  severe gastroenteritis, with fluid losses and electrolyte disturbance (low Na, K, Ca, Mg), hypotension and hypovolemic shock.
- Phase 2 (24 to 36 hours)
  multiple organ failure. Leucocytosis followed by pancytopenia; sepsis. Hepatic, respiratory, renal and circulatory failure, metabolic acidosis, rhabdomyolysis, DIC. Peripheral and central nervous system symptoms (mental status changes, sedation, delirium, seizures, coma; paralysis). Death from cardiovascular collapse.
- Phase 3 (day 6-14)
  Recovery, rebound leucocytosis, reversible alopecia.

Sauder P et al. Hum Toxicol 1983; 2: 169-73
Putterman C et al. Sem Arthritis Rheum 1991; 21: 143-55
Stern N et al. Schweiz Rdschau Med Praxis 1997; 86: 952-6

Outcome

Prognostic factors after oral ingestion

- reported dose ingested
  >0.5 mg/kg leads to significant morbidity (marrow aplasia)
  >0.9 mg/kg invariably fatal
  reported fatalities from 7 to 60 mg
  toxic blood concentrations >5 µg/L
- prothrombin time (lowest in first 3 days)
- WBC (highest in first 3 days)
- onset of cardiogenic shock (within 72 hours)

Baud FJ et al. Ann Emerg Med 1995
Bismuth C et al. J Toxicol Clin Exper 1986; 6: 33-8

Management

- Aggressive early gastrointestinal decontamination (SDAC / MDAC)
  HD / HP not useful (large V_d, protein binding)
- Intensive supportive care
  Fluid and electrolyte replacement
  Ventilatory and vasopressor support
  Blood and coagulation products
  Antibiotic treatment
- Filgrastim (G-CSF) 5 µg/kg/day.
- Immunotherapy with anti-colchicine antibodies (experimental; not available)

Bismuth C. Acta Clin Belg 1990; 45 suppl.13: 20-8
Katz R et al. Ann Pharmacother 1992; 26: 1087-8
Critchley JAHJ et al. Hum Exper Toxicol 1997; 16: 229-32

Management

Immunotherapy

- Goat anti-colchicine Fab fragments were effective in experimental and clinical colchicine poisoning.
- Redistribution from intracellular, with increase of plasma colchicine concentration, free colchicine undetectable.
- Rapid clinical improvement.
  480 mg colchicine-specific Fab for 60 mg colchicine (0.96 mg/kg)
- Not commercially available, but highly desirable.

Sabouraud AE et al. J Pharmacol Exp Ther 1992; 260: 1214-9
Baud FJ et al. NEJM 1995; 332: 642-5

Controversies

Controversy No. 1

- In acute gout, should colchicine be dosed until gastrointestinal symptoms occur ?

No, particularly not in intravenous administration !

Colchicine should be used by experienced prescribers only !

Controversies

Controversy No. 2

- Should colchicine still be used at all ?

With a therapeutic index of almost zero colchicine is a very prolematic substance.

There is still some evidence for the use in gout and in familial Mediterranean fever.

Controversies

Controversy No. 3

- Should anti-colchicine antibodies be made available commercially ?

From an economical point of view: Probably no.
(Low incidence of poisoning, severe cases mostly intentional. Prophylaxis might be more cost-effecive.)

From a medical point of view: Yes !
(Immunotherapy is the only causal treatment option)

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