Colchicine Poisoning

Diagnosis, management, and public health impact

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H. Kupferschmidt: Colchicine Poisoning

Pharmacology of colchicine

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

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.

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

- Absorption: rapid, incomplete? (oral bioavailability 25-50%); peak concentration 0.5 to 2 hours after dosing. Enterohepatic recirculation with biphasic plasma concentration.
- Vd = 2 L/kg; protein binding: 30-50%
- Elimination half-life = 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
- Tröger U et al. BMJ 2005; 331: 613
- Amoura Z et al. J Rheumatol 1994
- Goodman & Gilman’s 2006; Dollery C. 1991
- Galièr A et al. 1998: 25-30%
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Microtubules

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

Physiological role of microtubules
- Cytoskeleton
- Cellular polarity
- Cellular motility
- organelles
- proteins
- ciliae and flagellae
- cell migration
- Cellular transport
- Phagocytosis
- Mitosis

Dustin P. Microtubules, 1978

http://dept.kent.edu

Microtubule formation
Microtubule formation is extremely dynamic (half-life = 10 min.)

Colchicine blocks assembly of tubulin heterodimers

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 sarcoplasmic reticulum function and decrease in calcium myofilament sensitivity)
- neurotoxicity (impaired axonal transport and vesicle release)

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

Epidemiology


http://www.cytochemistry.net

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**Epidemiology**

**Plant ingestion**
- Occurs rarely but regularly
- Fatalties 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)

**Colchicine poisoning in Europe**
- E-mail based survey in all European Poisons Centres listed in the EAPCCCT 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

**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**

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

**Epidemiology: Europe**

- 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.
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: Europe

Epidemiology: U.S.

<table>
<thead>
<tr>
<th>YEAR</th>
<th>Tablets</th>
<th>Plant</th>
<th>Total</th>
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<tbody>
<tr>
<td>1999</td>
<td>146</td>
<td>24</td>
<td>170</td>
</tr>
<tr>
<td>2000</td>
<td>159</td>
<td>21</td>
<td>180</td>
</tr>
<tr>
<td>2001</td>
<td>195</td>
<td>25</td>
<td>220</td>
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<td>2002</td>
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<td>11</td>
<td>242</td>
</tr>
<tr>
<td>2004</td>
<td>310</td>
<td>22</td>
<td>332</td>
</tr>
<tr>
<td>2005</td>
<td>312</td>
<td>8</td>
<td>320</td>
</tr>
<tr>
<td>Total</td>
<td>1588</td>
<td>123</td>
<td>1711</td>
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<tr>
<td>Average</td>
<td>226.9</td>
<td>17.6</td>
<td>244.4</td>
</tr>
</tbody>
</table>

Epidemiology: U.S.

Age groups, reason of exposure, and outcome

- Age groups

- Reason of exposure
  - Unintentional: 1045
  - Intentional: 317
  - Other: 3
  - ADR: 214

Epidemiology: U.S.

<table>
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<tr>
<th>Outcome</th>
<th>Total</th>
<th>Average</th>
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<tr>
<td>none</td>
<td>443</td>
<td>63.3</td>
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<tr>
<td>minor</td>
<td>283</td>
<td>40.4</td>
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<tr>
<td>moderate</td>
<td>189</td>
<td>26.9</td>
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<td>major</td>
<td>51</td>
<td>7.3</td>
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<tr>
<td>death</td>
<td>37</td>
<td>5.3</td>
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Epidemiology: U.S.

Total cases reported per year

Fatalities
- Of the 37 fatalities, none was due to Colchicum autumnale ingestion.
### Epidemiology

**Comparison Europe - U.S.**

- **Europe**
  - Population (millions): 580
  - Cases / million population: 0.26
  - Fatalities / million population: 0.017
  - 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

### 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.

### 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)

### Management

- **Aggressive early gastrointestinal decontamination (SDAC / MDAC)**
- HD / HP not useful (large Vd, 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)

- 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.

### Immunotherapy

- 480 mg colchicine-specific Fab for 60 mg colchicine (0.96 mg/kg)
- Not commercially available, but highly desirable.

### 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!
Controversy No. 2

Should colchicine still be used at all?

With a therapeutic index of almost zero colchicine is a very prometic substance. There is still some evidence for the use in gout and in familial Mediterranean fever.

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-effective.)

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

References

15. Critchley H. Kupferschmidt: Colchicine Poisoning
16. From a medical point of view: Yes ! (Immunotherapy is the only causal treatment option)
References