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COLCHICINE TOXICITY

By Amberly R. Johnson, PharmD and Neda Nourbakhsh, PharmD



Autumn Crocus

INTRODUCTION

Colchicine is a plant-based alkaloid derived from *Colchicum autumnale* (autumn crocus) and *Gloriosa superba* (glory lily).^{1,2} Historically colchicine was formulated alone or in combination with probenecid and available by intravenous and oral administration.⁴ Intravenous colchicine was removed from the market in 2009 after its use was associated with multiple adverse events, including death. Colchicine-only oral products were also removed from the market in 2009 after the FDA approved Colcrys®, an oral colchicine prescription product indicated for the treatment and

prophylaxis of gout and Familial Mediterranean fever (FMF). Exposures to colchicine-containing plants and pharmaceutical preparations continue to result in sig-

nificant morbidity and mortality due to colchicine's narrow therapeutic index. From 2009-2015, 2 618 exposures to colchicine-containing pharmaceutical products and 135 exposures to colchicine-containing plants were reported to US poison control centers.⁵⁻¹¹ The majority of these exposures were unintentional. Moderate effects occurred in 230 exposures to colchicine-containing pharmaceuticals and two exposures to colchicine-containing plants. Major effects occurred in 46 exposures to colchicine-containing pharmaceuticals. Twenty-four deaths related to ingestion of colchicine pharmaceutical products were reported during

this period.⁵⁻¹¹

Mechanism of Action/Toxicity

Colchicine is a microtubule toxin.^{1,12-14} Microtubules are needed for cell function, structure, and division. Colchicine binds to tubulin, the individual subunit of the microtubule, and prevents polymerization and elongation of the microtubule. This disrupts cell division and inhibits migration and secretion of chemokines and cytokines. Rapidly dividing cells are most commonly affected by colchicine; however, due to the ubiquitous nature of microtubules, all tissue types may be affected by colchicine.^{1,12-14}

Pharmacology

Colchicine is rapidly absorbed from the small intestine and undergoes extensive first-pass metabolism with 45% bioavailability.^{2,12} Colchicine reaches peak plasma concentrations at 1.5 hours post-ingestion (range 1-3 hours)

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and may exhibit a secondary peak 3-36 hours post ingestion due to enterohepatic recirculation.^{2,12}

Colchicine is lipophilic and has a large volume of distribution (5-8 L/kg).² It has minimal protein binding (39%).² Colchicine is metabolized by CYP3A4 to two inactive metabolites and primarily undergoes hepatobiliary excretion with less than 20% of the drug eliminated by the kidneys.^{2,12-14,15} The terminal half-life of colchicine is 26.6-31.2 hours in patients receiving repeated doses.²

Concomitant use of medications and certain medical conditions that affect colchicine's pharmacokinetics place patients at increased risk for toxicity. Medications that inhibit CYP3A4 (i.e., clarithromycin, erythromycin,

ketoconazole, grapefruit juice) result in increased serum and tissue colchicine concentrations.^{2,13,15} Medications that inhibit P-glycoprotein (i.e., clarithromycin, cyclosporine) result in increased absorption from the small intestine and decreased clearance of colchicine from the enterocyte.^{2,13,15} Patients with renal dysfunction or hepatic dysfunction may require colchicine dose adjustments, and concomitant use of colchicine and CYP3A4 or P-glycoprotein inhibitors in these patients is contraindicated.^{2,12,13,15}

Therapeutic Use

Colchicine is currently FDA-approved for the prophylaxis and treatment of gout and Familial Mediterranean fever (FMF).² Prior to 2009, (*cont. on pg. 2*)



New! Utah Poisoning Trends Online

The Utah Poison Control Center (UPCC), Utah's resource for accurate and up-to-date poison information, is excited to announce Toxic Trends. Toxic Trends is an online resource for current trends in poison exposures reported to the UPCC on specific topics of interest. The reports offer a visual representation that makes complex data more accessible, understandable, and usable.

The UPCC is pleased to provide this new resource. Check out this valuable information at <http://poisoncontrol.utah.edu/toxictrends.php>

(cont. from pg. 1)

Colchicine

colchicine was FDA-approved for the treatment of gouty-arthritis only when used in combination with probenecid²⁰; however intravenous and oral colchicine-only products were used off-label to treat a variety of inflammatory conditions, including FMF, pericarditis, amyloidosis, and Behcet's syndrome.^{16,17} In 2009, the FDA removed all IV colchicine preparations from the market after review of 50 adverse events, including 23 deaths, associated with intravenous colchicine through June 2007.^{14,15,17} Three of these deaths resulted from an eight-fold intravenous compounding error, and several of these deaths occurred in patients using IV colchicine as an alternative treatment for chronic back pain.^{14,17,18} Oral colchicine-only dosage forms were also removed from the market in 2009 when the FDA approved Colcris® based on data from the AGREE trial (Acute Gout Flare Receiving Colchicine Evaluation), a randomized placebo-controlled trial, which established lower cumulative dosing recommendations for colchicine.^{16,19} Patients with a qualifying gout flare (n=185 patients) were randomized to high-dose colchicine (1.2 mg, followed by 0.6 mg every 1 hour x 6 hours; max dose 4.8 mg), low-dose colchicine (1.2 mg, followed by 0.6 mg in 1 hour; max dose 1.8 mg), and placebo. Patients taking high-dose colchicine had less efficacy (32.7% vs. 37.8%) and more

side effects (76.9% vs. 36.5%) when compared to patients taking low-dose colchicine.¹⁹

Therapeutic colchicine dosing regimens vary among the treatment of FMF, acute gout attack, and gout prophylaxis. These regimens are listed in Table 1.1.^{2,20}

Recent dosing changes or variable dosing regimens may contribute to incorrect prescribing and therapeutic errors leading to unintentional colchicine toxicity.²¹

Clinical Effects in Toxicity

Colchicine toxicity can be divided into three overlapping phases.^{1,15,22} In the first phase of toxicity (0-24 hours post-ingestion), gastrointestinal toxicity is predominant with abdominal pain, diarrhea, nausea, and vomiting. Electrolyte abnormalities and hypovolemia may occur secondary to gastrointestinal fluid loss. Leukocytosis may also be present.^{1,15,22} Gastrointestinal effects are the most

common side effects from therapeutic use of colchicine,² and differentiating colchicine side effects from acute toxicity may be difficult.

Multi-organ dysfunction, metabolic derangements, and myelosuppression are predominant in the second phase of colchicine toxicity (1-7 days post-ingestion).^{1,15,22} Myocardial dysfunction, respiratory compromise, renal insufficiency, and hepatotoxicity may occur. Neurotoxic effects, including confusion, delirium, convulsions, encephalopathy, or coma, may be present. Marrow suppression resulting in coagulopathy, leukopenia, thrombocytopenia, and pancytopenia may occur. Metabolic acidosis and rhabdomyolysis may be present.^{1,15,22} Death secondary to fatal dysrhythmias, cardiovascular collapse, coagulopathies, or infection usually occurs during this phase of toxicity.^{15,22,23}

For surviving patients, the third phase of colchicine toxicity is known (cont. on pg. 4)

TABLE 1.1: Therapeutic Colchicine Dosing^{2,20}

Condition	Adult Dosing (> 12 years age)
Familial Mediterranean fever (FMF)	Colchicine 1.2-2.4 mg per day divided in 1-2 doses*
Acute gout treatment	Colchicine 1.2 mg at first sign of flare, followed by 0.6 mg in 1 hour; max dose 1.8 mg
Gout prophylaxis	Colchicine 0.6 mg once or twice daily; max dose 1.2 mg
Chronic gouty arthritis	Colchicine 0.5 mg/probenecid 500 mg 1 tablet daily x 1 week, then 2 tablets daily

*Pediatric dosing for FMF only: 4-6 yr.—colchicine 0.3-1.8 mg per day in 1-2 divided doses; 6-12 yr.—colchicine 0.9-1.8 mg per day in 1-2 divided doses

POISON PEARLS

HYPERNATREMIA FROM HOUSEHOLD PRODUCTS

By Kezia Brown, PharmD and
Kaitlyn Brown, PharmD

Sodium is found in many household products, including table salt, rock salt, baking soda, soy sauce, and home-made play dough. Internet searches yield do-it-yourself recipes for saline enemas, saltwater solutions to induce emesis, and baking soda preparations for acid reflux relief or to help pass a urine drug test. Sodium is often perceived by the public as being harmless, but both unintentional and intentional exposures can result in serious morbidity and mortality. Between the years 2000-2011, 29 059 cases of sodium exposures were reported to US poison control centers: 11 cases had major medical outcomes and 7 were fatal (4 children, 3 adults).¹

Hyponatremia is defined as a serum sodium concentration greater than 145 mEq/L. A toxic dose of sodium chloride is documented to range from 0.5-1 g/kg, with fatal doses ranging between 0.75-3.0 g/kg.²⁻⁴ Table 2.1 lists the sodium content of various household products.

TABLE 2.1:
Sodium in Common Household Products

Sodium Containing Product	Na (g)/tbsp
Table Salt	7.2
Baking Soda	2.86
Homemade play dough	4-6
Soy Sauce	0.9



Photo Credit: Dubravko Soric

Sodium is an oral mucosa and gastric irritant. Initial findings after acute toxicity include nausea, vomiting, abdominal cramping, and thirst.^{2,3} The increase in serum sodium results in increased serum tonicity (hypertonicity) and osmolarity (hyperosmolarity). Hypertonicity in the brain manifests with more severe neurologic symptoms, including lethargy,

neuromuscular weakness, seizures, cerebral hemorrhage, or death.^{2,3,5,6} Seizures can occur at any time in the clinical course with the probability of occurrence proportional to the serum sodium concentration.^{1,3,4,7-9} Patients with hyponatremia secondary to acute sodium bicarbonate ingestion are at risk of developing metabolic alkalosis, respiratory depression, hypokalemia, and cardiac dysrhythmias.⁶

Acute hyponatremia is managed by correcting serum sodium with hypotonic fluid.^{2,3} Recommended intravenous fluids include 5% dextrose and hypotonic saline (0.2% or 0.45%). Serum sodium should be corrected proportionally to the rate at which the imbalance occurred to minimize risk of cerebral edema from rapid changes in osmolarity.^{2,3} The risk of cerebral edema is low in acute hyponatremia (hyponatremia occurring over a period of hours), and it is acceptable to lower the serum sodium concentration at a rate of 1 mmol/L/hr.³ Patients with chronic hyponatremia have adjusted to the hyperosmolarity and are at a higher risk for developing cerebral edema if the serum sodium is adjusted too rapidly. Due to this increased risk, serum sodium should be reduced at a slower rate of

0.5 mmol/L/hr or 10 mmol/L/day.³ Benzodiazepines are the recommended first line of treatment for patients with seizure.

Hyponatremia can result from intentional and unintentional exposures to a number of household substances. Mild hyponatremia manifests with gastrointestinal symptoms, while more severe toxicity may result in seizure or cerebral hemorrhage. Treatment is primarily supportive and aimed at reducing the serum sodium concentration at an appropriate rate to avoid cerebral edema. Call the Utah Poison Control Center if you suspect a patient has sodium toxicity.



Homemade play dough products from three different recipes
Photo Credit: Nena Bowman

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Close up of a set M-44 device.

Photo Credit: Guy Connolly, U.S. Department of
Agriculture National Wildlife Research Center

M-44 Sodium Cyanide

The United States Department of Agriculture, Animal and Plant Health Inspection Service, Wildlife Services would like to remind you that M-44 sodium cyanide devices are used in Utah. The ejector device contains a capsule of sodium cyanide that is placed in the ground and scented with lure. This device is used in specific situations to control coyotes to protect livestock and endangered species. This device is primarily used on private lands but may also be used on federal land in any county in the state. Areas where the M-44 sodium cyanide device is used should be marked with signs. While human exposure to this device is extremely unlikely, be aware that it contains 91% sodium cyanide, which is potentially lethal. A recent case this year in Idaho involved a dog and a child who were accidentally exposed. The dog was killed immediately and the child required emergency care. If someone is exposed to a device that has discharged into them, call 911 immediately. Contact the Utah Poison Control Center for assistance in management with antidotes. Pets exposed should be taken immediately to an emergency veterinary provider.

(cont. from pg. 2)

Colchicine

as the recovery phase (7 days post-ingestion).^{1,15,22} Myelosuppression and organ dysfunction resolves. Risk of secondary infection remains high in leukopenic patients. Alopecia, myopathies, or neuropathies may be present.^{1,15,22}

Toxic Dose

The toxic dose of colchicine is not well defined.¹ A prognostic rule exists in most colchicine toxicology literature today that was developed by Bismuth and colleagues from several case reports in 1977.²⁴ They report 100% mortality with ingestions greater than 0.8 mg/kg, 10% mortality with ingestions 0.5–0.8 mg/kg, and 100% survival with ingestions less than 0.5 mg/kg. However, exceptions to this rule have been reported, including a case report of a 30-year-old man who died after ingesting 0.4 mg/kg (39.6 mg).²⁴

Monitoring

The following monitoring parameters are recommended for patients presenting with colchicine toxicity: baseline ECG, continuous cardiac monitoring and pulse oximetry, complete blood count (CBC), complete metabolic panel (CMP), arterial/venous blood gas, prothrombin time, creatinine kinase (CK), and troponin.^{1,15,23} Acetaminophen and salicylate concentrations are also recommended for patients when there is concern for self-harm.

Colchicine plasma concentrations are not readily available in the clinical setting, and the correlation between plasma colchicine concentration and the severity of toxicity is not established.¹⁵

Treatment/Management

There is no available antidote for colchicine toxicity. Treatment consists of aggressive decontamination followed by supportive care. Consider gastric lavage followed by activated charcoal for patients who present without vomiting 1–2 hours post-ingestion.^{1,15} Also consider multi-dose activated charcoal in patients without vomiting due to enterohepatic recirculation of colchicine.¹ Intubate and ventilate patients with respiratory compromise.^{1,15,22} Correct hypovolemia, electrolytes, and acid/base disturbances. Administer vasopressors for hemodynamic instability. Consider administering blood

products or granulocyte colony-stimulating factor (G-CSF) to patients with leukopenia or thrombocytopenia. Hemodialysis and hemoperfusion are ineffective treatments for colchicine toxicity due to colchicine's large volume of distribution, but they may help correct metabolic acidosis and electrolyte abnormalities in patients with acute renal failure.^{1,15,22}

Extracorporeal membrane oxygenation (ECMO) may be helpful in patients with refractory cardiovascular shock secondary to colchicine toxicity²⁵ as demonstrated by the case of a 68-year-old woman who developed shock and multi-organ failure after eating *Colchicum autumnale* she mistook for wild leek.²⁶ The patient was placed on venous-arterial extracorporeal membrane oxygenation (VA-ECMO) three days post-ingestion. Her cardiac function improved on day nine, and she was decannulated on day 10. Her cardiovascular course was further complicated by a cardiac arrest on day 12; however, she made a complete recovery and was discharged from the ICU 24 days post-ingestion.²⁶

The use of colchicine-specific Fab fragments in humans has been reported once in literature, but these are not available for human use. In France, goat colchicine-specific Fab fragments were administered to a 25-year-old woman after reportedly ingesting a potentially fatal dose of colchicine (0.96 mg/kg).²⁷ The patient survived and was discharged on hospital day 25. Recently in Australia, ovine colchicine-Fab fragments were used in a rat model.²⁸ Rats treated with colchicine-specific Fab fragments eliminated more colchicine in the urine (26.1 mg/ml) compared to saline (6.3 mg/mL). Colchicine-specific Fab fragments are not expected to be commercially available, and their future clinical utility is unknown.

Conclusion

Colchicine has a narrow therapeutic index. The toxic dose is not well established, and significant adverse effects, including death, have occurred from unintentional and intentional exposures. Management consists of aggressive decontamination and supportive care in an ICU setting. The Utah Poison Control Center is available for consultation at 1-800-222-1222, 24 hours a day, 7 days a week, for any case of colchicine toxicity.

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TOXINS IN THE NEWS

TEETHING TABLETS

By B. Zane Horowitz, MD



In October 2010, the FDA issued a safety warning about teething tablets, labeled as homeopathic, which contained belladonna because of concern for toxicity in infants. This was because belladonna, which comes from the deadly nightshade plant, contains atropine and scopolamine, both anticholinergic substances. Atropine is not indicated for use in infants for teething since cases of seizures have been published in literature with use of atropine-containing products in very young infants.¹ More recently, homeopathic teething tablets and gels by Standard Homeopathic Company, the makers of Hyland's brand, have been found once again to contain

belladonna. Only a few lots of teething tablets were analyzed, and although many were found to contain no atropine or scopolamine, atropine concentrations as high as 1,100 ng and scopolamine concentrations as high as 390 ng were found in one tablet each.² It is worth noting that several other compounds, including crude coffee, calcium phosphate, and chamomile, were also found in various and inconsistent quantities between tablets.³

Often, teething-aid products are advertised as natural and homeopathic. That homeopathic medications could cause a problem may seem perplexing since the theory behind homeopathy is to do successive dilutions of an active compound ingredient until only the "memory" of that compound exists. The compounds labeled 12X in homeopathic nomenclature should have been diluted down 100-fold, 12 times, leaving insignificant trace amounts only; however, atropine concentrations were found in some of these products, albeit below the level expected to produce symptoms.

Since the original safety warning, the FDA has grown more concerned about teething tablets. After a report by a father of a child who developed status epilepticus after using teething tablets, the FDA found over 400 adverse events reported with their use.⁴ These

products have now been taken off the market; as of April 13, 2017, Hyland's has now recalled existing distributed lots, so parents may still have some in their medicine cabinets. Consumers who have Standard Homeopathic Company products that are being recalled should contact the company at 1-800-991-3376. Other companies' teething products, including CVS and Raritan brands, had already been recalled out of concern for safety.

While there is some disagreement on what to do for a teething child, using teething tablets or gels that contain atropine, scopolamine, or even benzocaine (used in some teething preparations) carries an unacceptable risk to the child.

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OUTREACH EDUCATION

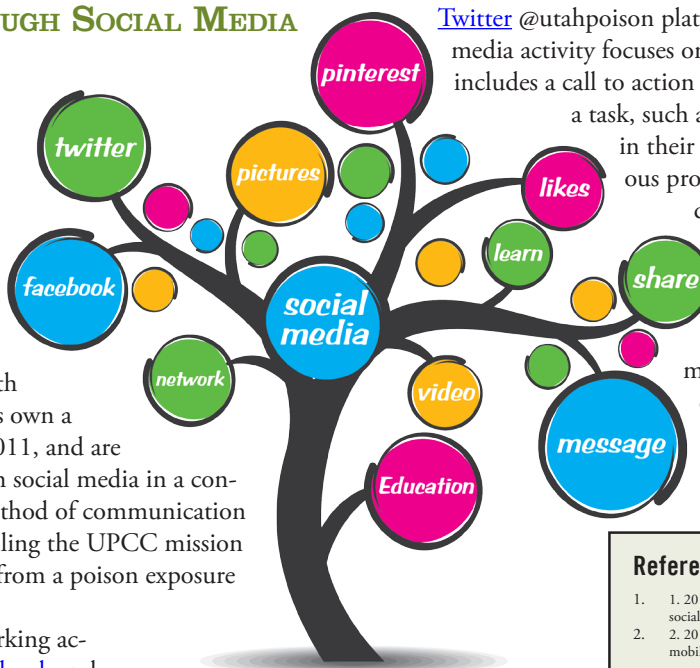
POISON PREVENTION THROUGH SOCIAL MEDIA

By Sherrie Pace, MS, MCHES

The Utah Poison Control Center (UPCC) fosters a social media program that is managed by our outreach education team since social media provides a public platform to share messages about poison topics. Research indicates that 7 out of 10 Americans use social media to not only connect socially but to access news and share information with others.¹ Furthermore, 77% of Americans own a smartphone, an increase from 35% in 2011, and are better able to access information through social media in a convenient way.² Using social media as a method of communication is an increasingly important part of fulfilling the UPCC mission to prevent and minimize adverse effects from a poison exposure through education, service and research.

Photos, videos and other social networking activities are promoted on the UPCC [Facebook](#) and

[Twitter](#) @utahpoison platforms. The majority of our social media activity focuses on poison prevention and often includes a call to action that encourages readers to complete a task, such as saving the poison hotline number in their phone or storing potentially hazardous products up and out of reach of children. In a continued effort to reach the community, UPCC will expand social media outreach in 2017 by launching a Pinterest account. This image-focused social media platform will provide further opportunity for people to view our infographics and other photos promoting poison prevention.



References

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WARNING

PEDIATRIC ACETAMINOPHEN CHEWABLE DOSING CHANGE

Many manufacturers and retailers of pediatric acetaminophen solid dose medicines are transitioning to a single strength of 160 mg chewables in the United States to be named "Children's."

This transition is consistent with a 2011 FDA Advisory Committee recommendation that the FDA consider a single strength for solid pediatric acetaminophen products. It is intended to help minimize the potential for medication errors due to confusion between multiple strengths.

Important points:

- Currently the marketplace includes pediatric acetaminophen chewable products available in both 80 mg and 160 mg strengths. These are commonly referred to as "Children's" and "Junior" respectively.
- The in-store transition to the single-strength 160 mg acetaminophen chewable products will begin in early 2017 and is anticipated to continue throughout 2017. However, the transition within any caregivers' medicine cabinet may take considerably longer.
- Verify the acetaminophen product strength (160 mg or 80 mg) a parent or caregiver is using before providing dosing directions.

MEET THE UPCC STAFF



PAUL HINCKLEY, PHARM.D, CSPI, is originally from Utah, but after earning his doctorate of pharmacy from the University of Utah (including a rotation with the Utah Poison Control Center (UPCC)) he moved to Alaska to work for the Indian Health Service in Anchorage. Paul returned to Utah after getting a job offer with the UPCC in August 2015, and, while he misses living in Alaska, he is happy with the move. In his free time, Paul enjoys hiking, hockey, traveling, reading and building things. Paul's toxicology interests include toxic alcohols and diabetes medications.



BRITTANI PETERSEN, PHARM.D, CSPI, began working at Utah Poison Control Center (UPCC) in September 2015. She grew up in Altoona, Iowa, and was first introduced to a career in pharmacy during high school. She was a cashier and did insurance reconciliation at a local pharmacy. She did her undergraduate work at Brigham Young University and Utah Valley University while working as a pharmacy technician before pursuing a PharmD at the University of Utah. After graduation, she worked as a retail pharmacist until she joined the UPCC. Brittani enjoys many different aspects of pharmacy, and working at UPCC has helped further cultivate her love for learning since there is no shortage of new information in the world of toxicology. Outside of work, Brittani loves spending time with her husband, three kids, and extended family. She enjoys being outside, camping, and reading. Her interests in toxicology include cardiac medications and drugs that can be deadly in a single dose.

UTAH POISON CONTROL CENTER STAFF

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