INTRODUCTION

Colchicine, podophyllotoxin, and the vinca alkaloids exert their primary toxicity by binding to tubulin and interfering with microtubule structure and function. The ubiquitous nature of microtubules within human cells and the heavy reliance on them for maintenance of normal cell functions present numerous opportunities for these xenobiotics to cause dysfunction at a cellular, organ, and organ system level in a dose-dependent fashion. This chapter discusses the history, pharmacology, pharmacokinetics, toxicokinetics, pathophysiology, toxic dose, clinical manifestations, diagnostic testing and management of toxicity resulting from these xenobiotics both during therapeutic use and in the overdose setting. Because some information is limited, not all of the aforementioned topics will be discussed for each xenobiotic.
COLCHICINE

History

The origins of colchicine and its history in poisoning can be traced back to Greek mythology. Medea was the evil daughter (and a known poisoner) of the king of Colchis, a country that lay east of the Black Sea in Asia Minor. After being betrayed by her husband Jason (of Jason and the Argonauts), she killed their children and her husband’s lover. Medea used plants of the Liliaceae family, of which *Colchicum autumnale* is a member, to poison her victims.\(^{20,132,172}\) The use of colchicum for medicinal purposes is reported in *Pedanius Dioscorides De Materia Medica*, an ancient medical text, written in the first century A.D.,\(^ {132}\) and subsequently in the 6th century A.D. by Alexander of Tralles, who recommended it for treating arthritic conditions.\(^ {110}\) However, colchicum fell out of favor, perhaps because of its pronounced gastrointestinal (GI) effects, until it was introduced for “dropsy” and various other nonrheumatic conditions in 1763.\(^ {20,172}\) In the late 18th century, a colchicum-containing product known as *Eau Medicinale* appeared, which reportedly had strong antigout effects.\(^ {172}\) Colchicine, the active alkaloidal component in colchicum, was isolated in 1820 and rapidly became popular as an antigout medication.\(^ {132,172}\) Benjamin Franklin reportedly had gout and is credited with introducing colchicine in the United States.\(^ {132}\) Colchicine is still used in the acute treatment and prevention of gout and is used in other disorders, including amyloidosis, Behçet’s syndrome, familial Mediterranean fever, pericarditis, arthritis, pulmonary fibrosis, vasculitis, biliary cirrhosis, pseudogout, certain spondyloarthropathies, calcinosis, and scleroderma.\(^ {11,20,121,125}\) Systematic data supporting the efficacy of colchicine therapy in many of these other diseases are lacking.

Colchicine is derived from two plants of the Liliaceae family, *C. autumnale* (autumn crocus, meadow saffron, wild saffron, naked lady, son-before-the-father) and *Gloriosa superba* (glory lily).\(^ {172}\) The autumn crocus contains different amounts of colchicine by weight, depending on the plant part (bulb, 0.8%; flowers, 0.1%; seeds, 0.8%; and the corm or underground stem, 0.6%).\(^ {110,132,151}\) Colchicine concentrations within the plant peak during the summer months.\(^ {132}\) The leaves of *C. autumnale* closely resemble those of the *Allium ursinum* or wild garlic and are mistaken for them.\(^ {39,40,98}\) The tubers of *G. superba* were confused with *Ipomoea batatas* (sweet potatoes) in one report\(^ {172}\) (Chap. 118).

There is a dearth of good epidemiologic data on colchicine poisoning. The American Association of Poison Control Centers records several hundred overall exposures annually (Chap. 130). The majority of these exposures are in adults and are categorized as unintentional. Of the cases with a recorded outcome, approximately 10% have evidence of moderate or major toxicity or resulted in death.\(^ {36}\) A limited number of cases are caused by intentional suicidal ingestions with colchicine and therapeutic colchicine administration has contributed to adverse health effects, and in some cases death, among hospitalized patients (probably related to failure to adjust dosing for renal impairment).\(^ {147}\) At least 50 adverse events (23 of which were fatalities) were linked to the use of intravenous (IV) colchicine.\(^ {4}\) The United States Food and Drug
Administration ordered companies to stop the marketing of unapproved injectable drug compounds containing colchicine in 2009. Serious questions remain about the utility of colchicine in light of its extremely narrow therapeutic index.

**Pharmacology**

Colchicine is a potent inhibitor of microtubule formation and function that interferes with cellular mitosis, intracellular transport mechanisms, and maintenance of cell structure and shape. The ubiquitous presence of microtubules in cells throughout the body presents a wide variety of targets for colchicine in poisoning. Colchicine accumulates in leukocytes and has inhibitory effects on leukocyte adhesiveness, ameboid motility, mobilization, lysosome degranulation, and chemotaxis. At doses used clinically, colchicine inhibits neutrophil and synovial cell release of chemotactic glycoproteins. Colchicine also inhibits microtubule polymerization, which disrupts inflammatory cell-mediated chemotaxis and phagocytosis. It reduces expression of adhesion molecules on endothelial and white blood cells (WBCs) and affects polymorphonuclear cell cytokine production. Colchicine also acts as a competitive antagonist at GABA<sub>A</sub> receptors.

**Pharmacokinetics and Toxicokinetics**

Colchicine is rapidly absorbed in the jejunum and ileum and has a bioavailability generally between 25% and 50%. It is highly lipid soluble with a volume of distribution that ranges from 2.2 to 12 L/kg, and is reported to increase to 21 L/kg in overdose. Colchicine binding to plasma proteins approaches 50%. Protein binding is principally to albumin, although some binding to α<sub>1</sub>-acid-glycoprotein and other lipoproteins is reported. 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. Peak serum concentrations after ingestion occur between 1 to 3 hours. Toxic effects usually do not occur with concentrations less than 3 ng/mL.

Colchicine is primarily metabolized through the liver with up to 20% of the ingested dose excreted unchanged in the urine. Colchicine undergoes demethylation by CYP3A4. Detoxification mainly occurs through deacetylation, demethylation, biliary secretion, and excretion in the stool. Enterohepatic recirculation of colchicine occurs.

Studies reporting on the serum colchicine elimination half-lives range from 9 to 108 minutes. On closer examination, however, these times probably more accurately reflect a rapid initial distribution phase. The drug undergoes a more delayed terminal elimination phase, which ranges from 1.7 to 30 hours, depending on the individual compartment model used to estimate elimination and the amount of colchicine absorbed. These values are on the same order as, and probably reflect the tubulin-
Colchicine complex disassociation time. Individuals with end-stage kidney disease and liver cirrhosis have elimination half-lives that are prolonged up to 10-fold. Colchicine remains in measurable quantities in certain tissues for a long time, as evidenced by its detection in WBCs after 10 days and in urine 7 to 10 days after exposure. Colchicine crosses the placenta and is secreted in breast milk, but it is not dialyzable. Postmortem examination of colchicine-poisoned patients reveals high concentrations within the bone marrow, testicles, spleen, kidney, lung, brain, and heart.

**Drug Interactions**

Colchicine metabolism is susceptible to drug interactions. Because colchicine is detoxified by CYP3A4, blood concentrations are susceptible to xenobiotics that alter the function of this enzyme, such as erythromycin, clarithromycin, and grapefruit juice. In particular, coadministration of clarithromycin and colchicine, especially in patients with chronic kidney disease, increases the risk of fatal interaction. P-glycoprotein (P-gp) expels and clears colchicine, and drugs that inhibit P-gp directly affect the amount of colchicine eliminated and hence toxicity. For example, cyclosporine increases colchicine toxicity. Coadministration of colchicine with statin or fibrate drugs, cyclosporine, ketoconazole, ritonavir, verapamil ER, diltiazem ER, fluindione (vitamin K antagonist) and nephrotoxic xenobiotics such as nonsteroidal antiinflammatory drugs and angiotensin-converting enzyme inhibitors has resulted in colchicine poisoning. Concomitant administration of P-gp or CYP3A4 inhibitors and colchicine should be avoided in patients with abnormal renal or hepatic function. If treatment with a P-gp or a strong CYP3A4 inhibitor is required in patients taking colchicine with normal renal or hepatic function, a dose reduction or temporary cessation of colchicine treatment should be considered.

**Pathophysiology**

Microtubules play a vital role in cellular mitosis and possess a high amount of dynamic instability. Microtubules are made up of tubulin protein subunits, of which three are known to exist: α, β, and γ. These structures are highly dynamic with α-β tubulin heterodimers, constantly being added at one end and removed at the other. Microtubules undergo two forms of dynamic behavior: dynamic instability, in which microtubule ends switch between growth and shortening phases, and treadmilling, in which there is a net growth (addition of heterodimers) at one end and a shortening (loss) at the other. Assembly and polymerization dynamics are regulated by additional proteins known as stabilizing microtubule-associated proteins (MAPs) and destabilizing MAPs. These dynamic behaviors and a resultant equilibrium are needed for multiple cell functions, including cell support, transport, and mitotic spindle formation for cell replication. Xenobiotics that bind to specific regions on tubulin can interfere with microtubule structure and function, thereby possibly causing mitotic dysfunction and arrest. This leads to cellular dysfunction and death. Xenobiotics that target microtubules can be generally divided into
two categories: polymerization inhibitors (ie, vinca alkaloids, colchicine) and polymerization promoters (ie, taxanes, laulimalides).25

Colchicine binds to a tubulin dimer at a specific region known as the *colchicine-binding domain*, which is located at the interphase of the α and β subunits of the tubulin heterodimer.25,99 This binding is relatively slow, temperature dependent, and generally irreversible, resulting in an alteration of the protein’s secondary structure.99,116,131 Colchicine binds at a second reversible but lower affinity site on tubulin.116,131 Current evidence suggests that the colchicine–tubulin complex binds to the microtubule ends and prevents further growth by sterically blocking further addition of dimers.25 Conformational changes in the tubulin and colchicine complex also result as colchicine concentrations increase, which weakens the lateral bonds at the microtubule end.25,175 Lateral and longitudinal interactions between dimers within a microtubule help stabilize the structure. The number of colchicine–tubulin dimers incorporated into the microtubule determines the stability of the microtubule ends.25 All of these processes prevent adequate binding of the next tubulin subunit and result in cessation of microtubule growth.139,188 Whereas at low concentrations, colchicine arrests microtubule growth, at high concentrations, colchicine actually causes microtubule depolymerization through disassociation of tubulin dimers.25

These conformational changes ultimately result in disassembly of the microtubule spindle in metaphase of cellular mitosis, cellular dysfunction, and death.81,99,116,163,183 The effects of colchicine are dose dependent, with high concentrations inhibiting further microtubule polymerization, as well as inducing depolymerization of already formed microtubules.128 Low concentrations can simply affect new microtubule formation and have no effect on preestablished polymer mass.128 Colchicine also inhibits microtubule-mediated intracellular granule transport.20,125

**Toxic Dose**

The toxic dose for colchicine is not well established. An early case series suggested that patients with ingestions of greater than 0.8 mg/kg uniformly died and those with ingestions above 0.5 mg/kg but less than 0.8 mg/kg would survive if given supportive care.28 This information was based on a limited series of patients and is not necessarily generalizable.148 More recent literature suggests that severe toxicity and even death occurs with doses smaller than 0.5 mg/kg, and conversely, some patients survive ingestions reported to be in excess of 0.8 mg/kg.71,145,148 This inability to accurately quantify the toxic dose in humans is likely due in great part to difficulty in dose estimation from the patient’s history and significant advances in supportive care. Furthermore, 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.

**Clinical Presentation**
The clinical findings among colchicine poisoned patients are commonly described as triphasic (Table 34-1). GI irritant effects, such as nausea, vomiting, abdominal distress, and diarrhea, occur within several hours after an overdose and lead to severe volume depletion. This first stage usually persists for 12 to 24 hours after ingestion. The second stage is characterized by widespread organ system dysfunction, particularly the bone marrow, and lasts for several days. The final phase is characterized by recovery or death, and the progression is usually defined within 1 week.

After overdose, the hematopoietic effects of colchicine are characterized by an initial peripheral leukocytosis, which is often as high as 30,000/mm³. This is followed by a profound leukopenia, which is classically lower than 1,000/mm³. It is commonly accompanied by pancytopenia, usually beginning 48 to 72 hours after overdose. The hematopoietic manifestations occur as a result of colchicine’s effects on bone marrow cell division. A rebound leukocytosis and recovery of all cell lines occur if the patient survives.
TABLE 34–1
Colchicine Poisoning: Common Clinical Findings, Timing of Onset, and Treatment

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

aThe interval time course is not absolute, and overlap of symptom presentations occurs.

ARDS = acute respiratory distress syndrome; EMG = electromyography; G-CSF = granulocyte-colony stimulating factor; GI = gastrointestinal; ICU = intensive care unit; IV = intravenous.

Colchicine toxicity is associated with the development of dysrhythmias and cardiac arrest. ⁸⁴ ¹⁰³ Complete AV block occurred in a child who ingested 0.4 to 0.5 mg/kg. ⁷⁸ In a rabbit model, colchicine results in a dose–dependent reduction in effective refractory period while maintaining a stable repolarization period and increased inducibility of ventricular fibrillation. ⁸⁴ Sudden cardiovascular collapse from colchicine typically occurs between 24 to 36 hours after ingestion. ¹³⁸ ¹⁴⁸ Profound hypovolemia and shock contribute to this collapse, ¹⁴⁸ but colchicine has direct toxic effects on skeletal and cardiac muscle, causing rhabdomyolysis. ³¹ ¹⁴⁹ ²¹⁰

Myopathy, ²²⁰ neuropathy, ¹² ¹²⁸ and a combined myoneuropathy ¹⁰, ⁵⁵, ¹²⁴, ¹⁹³ result from both long-term therapy and acute poisoning. ¹²⁸ A combined myoneuropathy is reported more often, with myopathy
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. Patients present with proximal limb weakness, distal sensory abnormalities, distal areflexia, and nerve conduction problems consistent with an axonal neuropathy. A small amount of myelin degeneration is reported on autopsy, which suggests a myelinopathic component. The myopathy is characterized by vacuolar changes on biopsy and accompanied by lysosome accumulation. Elevated serum creatine kinase activity is present concurrently with symptoms. 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.

Acute respiratory distress syndrome (ARDS) occurs with colchicine toxicity. The cause is not well understood but probably results from several factors, including respiratory muscle weakness, multisystem organ failure, and possibly direct pulmonary toxicity. Other indirect effects of colchicine include acute kidney injury and various electrolyte abnormalities.

Alopecia, which is usually reversible, is a well-described complication that occurs 2 to 3 weeks after poisoning in survivors. Dermatologic complications range in severity from 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, disseminated intravascular coagulation, pancreatitis, and liver dysfunction.

Although uncommon, poisoning from IV colchicine administration has occurred. Clinical and laboratory manifestations are similar to those that occur after oral overdose, including multisystem organ dysfunction and cytopenias.

Colchicine does not appear to be a significant human teratogen, but the limited work on this subject is not definitive.

**Testing**

Colchicine concentrations in body fluids are not available in a clinically relevant fashion and have no well-established correlation with severity of illness. However, effective steady-state serum concentrations for
treatment of patients with various illnesses are reported as 0.5 to 3.0 ng/mL. Concentrations greater than 3.0 ng/mL are associated with toxicity depending on the clinical situation, and concentrations greater than 24 ng/mL are definitely associated with poisoning. Serum concentrations do not correlate well with the amount of xenobiotic ingested in massive oral overdose settings. Initial laboratory monitoring should include a complete blood count (CBC), serum electrolytes, renal and liver function tests, creatine kinase, phosphate, calcium, magnesium, prothrombin time, activated partial thromboplastin time, and urinalysis. Other laboratory studies, such as a troponin, arterial blood gases, lactate, fibrinogen, and fibrin split products, are helpful in guiding care if cardiotoxicity, ARDS, or coagulopathies, respectively, are present. If cardiotoxicity is present or suspected, serial troponin concentrations (every 6–12 hours) are recommended.

There is an association between increasing concentrations and cardiovascular collapse. An electrocardiogram and chest radiograph should also be obtained. Serial CBCs are reasonable (at least every 12 hours) to evaluate for the development of depression in cell lines. Bile appears to be the biological matrix of choice for postmortem testing, probably because of normal postmortem biological processes that can increase blood colchicine concentration. One colchicine-associated fatality who had a premortem blood colchicine concentration of 50 ng/mL also had a postmortem femoral blood concentration of 137 ng/mL and a bile concentration greater than 600 ng/mL. Another reported a postmortem blood concentration of 60 ng/mL. Two IV colchicine-associated fatalities had postmortem blood colchicine concentrations of 32 and 44 ng/mL.

Management

Treatment for patients with colchicine toxicity is mainly supportive, which includes IV fluid replacement, vasopressor use, hemodialysis (for acute kidney injury, not for toxin removal), antibiotics for suspected secondary infection, colony-stimulating factors, and adjunctive respiratory therapy (endotracheal intubation, positive end-expiratory pressure) as indicated. Consultation with nephrology and hematology specialists should be obtained in the case of impaired renal function or evidence of hematologic toxicity. In severe, refractory poisoning, it is reasonable to attempt options such as intraaortic balloon pump therapy and extracorporeal membrane oxygenation therapy.

Because most patients with an acute oral colchicine overdose present several hours after their ingestion, vomiting has already begun, and the utility of GI decontamination is inadequately defined. However, given the extensive morbidity and mortality associated with colchicine overdose, orogastric lavage is most helpful and is reasonable in patients presenting within 1 to 2 hours of potentially life-threatening ingestions, who have no contraindications, are not already vomiting, and for which the physician is proficient in the procedure. 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 of colchicine is one
of the most beneficial interventions for this exceptionally grave poisoning. The delay in presentation to a health care facility coupled with the fact that patients often have GI symptoms such as vomiting significantly complicates using MDAC. Antiemetic medications will control emesis and facilitate AC administration.

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 poisoning. In colchicine-poisoned rats, anticolchicine Fab fragments caused a rapid 7.1-fold increase in serum colchicine concentration followed by increased urinary excretion of both colchicine and Fab anticolchicine. The increased urinary excretion of these fragments was associated with reversal of colchicine-induced diarrhea. In the single human case report, administration of anticolchicine Fab fragments 40 hours after a 0.96-mg/kg colchicine ingestion was temporally associated with a dramatic improvement in clinical and hemodynamic status. This improvement was also associated with a significant increase in serum colchicine concentrations, which suggests a redistribution of drug into the intravascular space. Unfortunately, this therapy is not commercially available.

Granulocyte-colony stimulating factor (G-CSF) is useful in the treatment of patients with colchicine-induced leukopenia and thrombocytopenia. The 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.

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.

Because of the significant morbidity and mortality associated with colchicine toxicity, all symptomatic patients with suspected or known overdoses should be admitted to the hospital for observation. Because these patients have a risk of sudden cardiovascular collapse within the first 24 to 48 hours, intensive care unit monitoring is recommended for at least this initial time period. A troponin concentration is recommended every 6 to 12 hours during this period because increasing results suggest an increased risk of cardiotoxicity and cardiovascular collapse. Blood cell counts should be followed at least daily to watch for cytopenias. Poisoned patients manifest GI signs and symptoms within several hours of ingestion and should be observed for at least 8 to 12 hours. Patients who do not manifest GI signs and symptoms within that time period after ingestion are unlikely to be significantly poisoned.

PODOPHYLLUM RESIN OR PODOPHYLLIN

History
Podophyllin is the name often used to refer to a resin extract from the rhizomes and roots of certain plants of the genus Podophyllum. Examples include the North American perennial Podophyllum peltatum (mayapple or mandrake), the related Indian species Podophyllum emodi, and the Taiwanese Podophyllum pleianthum (Chap. 118). It is more descriptive to refer to it as podophyllin resin, or podophyllin, contains at least 16 active compounds. These include a variety of lignins and flavonols, including podophyllotoxin, picropodophyllin, α- and β-pellatins, desoxypodophyllotoxin, and quercetin. Podophyllotoxin, a component of podophyllin, is a potent microtubular poison, similar to colchicine, and causes similar effects in overdose.

The first reported modern era medicinal use of podophyllin preparations was as a laxative in the 19th century. Its cathartic properties, as well as its potential toxicity, were noted as early as 1890, when the first fatality from podophyllin was recorded. Podophyllin was used to treat individuals with a variety of other health issues, including liver disease, scrofula, syphilis, warts, and cancer. Etoposide and teniposide are semisynthetic derivatives of podophyllotoxin used as chemotherapeutics.

Poisoning usually is caused by systemic absorption after topical application, after ingestion of the resin or plant, and after consumption of a commercial preparation of the extract. Systemic toxicity is described after unintentional dispensing of the incorrect herb, as well as after ingestion of herbal preparations containing podophyllin.

**Pharmacology**

Podophyllin is primarily used in modern pharmacopeia as a topical treatment for patients with verruca vulgaris and condyloma acuminatum. The active ingredient is believed to be podophyllotoxin. Podophyllotoxin exists in the plant as a β-D-glucoside. Numerous synthetic and semisynthetic derivatives of podophyllotoxin exist; however, the most important are probably the chemotherapeutics etoposide and teniposide. The antitumor effect of etoposide and teniposide results from their interaction with topoisomerase II and free radical production, leading to DNA strand breakage, an effect not shared by podophyllin and colchicine. Use of etoposide and teniposide leads to a cessation of cell growth in the late S or early G2 phase of the cell cycle. Further discussion of these xenobiotics can be found in the Chap. 50.

**Pharmacokinetics and Toxicokinetics**

Very limited information exists regarding the pharmacokinetics (absorption, distribution, metabolism, and elimination) of podophyllin as a preparation or for its major active ingredient, podophyllotoxin.

Podophyllotoxin is highly lipid soluble and easily crosses cell membranes.
Absorption of podophyllotoxin was measured in seven men after application of various amounts of a 0.5% ethanol podophyllotoxin preparation for condylomata acuminata.\textsuperscript{211} 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).\textsuperscript{211} Patients treated with less than or equal to 0.05 mL had 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.\textsuperscript{211}

**Pathophysiology**

The components of podophyllin have numerous actions within the cell, including inhibition of purine synthesis, inhibition of purine incorporation into RNA, reduction of cytochrome oxidase and succinoxidase activity, and inhibition of microtubule structure and function.\textsuperscript{46,86,214} Podophyllotoxin causes its toxicity similar to colchicine\textsuperscript{63,221} because it is able to bind to tubulin subunits and interfere with subsequent microtubule structure and function.\textsuperscript{63,221} Interestingly, radiolabeled podophyllotoxin inhibits colchicine binding to tubulin, suggesting that their binding sites overlap.\textsuperscript{63} Podophyllotoxin binds more rapidly than colchicine, and binding is reversible in contrast to colchicine.\textsuperscript{63} Podophyllotoxin also inhibits fast axoplasmic transport similar to colchicine by interference with microtubule structure and function.\textsuperscript{165,208} Many other compounds, such as the vinca alkaloids, cryptophycins, and halichondrins, also inhibit microtubule polymerization in a similar manner.\textsuperscript{117}

**Toxic Dose**

The minimum toxic dose associated with podophyllin ingestion is unknown. Limited information on the situations surrounding the few case reports of podophyllin poisoning that do exist does not provide sufficient detail from which to estimate it.

**Clinical Presentation**

Poisoning is described after ingestion,\textsuperscript{42} as well as after absorption from topical application of podophyllin.\textsuperscript{137,142} Toxicity also is reported after IV administration of podophyllotoxin\textsuperscript{94} and ingestion of mandrake root or herbal remedies containing podophyllin.\textsuperscript{68,83,219} Nausea, vomiting, abdominal pain, and diarrhea usually begin within several hours after ingestion.\textsuperscript{137,142,196} Symptoms of poisoning is often delayed for 12 hours or more after topical exposure to podophyllin and are typically caused by improper usage (excessive topical exposure, interruption in skin integrity, or failure to remove the preparation after a short time period).\textsuperscript{137,140,190} Initial clinical findings are not necessarily dictated by the route of exposure.\textsuperscript{137}
Alterations in central and peripheral nervous system 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 have occurred during the initial presentation. Patients developed paresthesias, lost deep tendon reflexes, and developed a Babinski sign. Cranial nerve involvement, including diplopia, nystagmus, dysmetria, dysconjugate gaze, and facial nerve paralysis, are all reported. Patients who recover from the initial event are at risk of developing a peripheral sensorimotor axonopathy. The reported duration for recovery from podophyllin-induced axonopathy is variable but is likely to take several months. Dorsal radiculopathy and autonomic neuropathy are reported. A myelopathic component in the neuropathy is reported.

Hematologic toxicity from podophyllin most likely results from its antimitotic effects. A review of the limited literature suggests that it is similar to colchicine but is not nearly as consistent in its pattern, severity, and frequency. An initial leukocytosis commonly occurs after poisoning, which is followed by leukopenia, thrombocytopenia, or generalized pancytopenia. In patients who recover, cell lines tend to reach their nadir within 4 to 7 days after exposure.

Other complications of poisoning include fever, ileus, elevated liver function test results, hyperbilirubinemia, coagulopathy, seizures, and acute kidney injury. Teratogenic effects resulting from exposure during pregnancy are reported.

**Testing**

Podophyllin or podophyllotoxin concentrations are not readily available. Routine testing for suspected or known podophyllin poisoning should include routine laboratory tests and other targeted testing as needed. Serial cell blood counts should be obtained in cases of poisoning to evaluate for pancytopenia.

**Management**

Management primarily consists of supportive and symptomatic care. If the patient presents within the first several hours of ingestion, a dose of AC is reasonable. Any topically applied podophyllin should be removed and the area thoroughly cleansed. Patients either progress to multisystem organ dysfunction and death or recover with supportive care. Blood cell counts should be monitored similarly to colchicine poisoning (at least daily).

A few case reports of treatment with extracorporeal elimination techniques exist. These reports include resin hemoperfusion and charcoal hemoperfusion. The role these procedures played in the patients' clinical courses is unclear. As a result, given the lack of evidence and potential risk, they cannot be routinely recommended at this time.
Patients with significant ingestions of podophyllin develop GI symptoms within a few hours, but patients have also presented with primarily neurologic symptoms, such as confusion or obtundation. The onset of toxicity is reported to be delayed as long as 12 hours after ingestion. Dermal exposure results in even further delayed onset of toxicity because systemic absorption is delayed and symptom onset is more insidious. 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.

VINCIRISTINE AND VINBLASTINE

History

More than 150 different alkaloidal compounds have been isolated from the periwinkle plant (Catharanthus roseus), most of which were used throughout history to manage illness from a variety of medical disorders, including cancer, scurvy, diabetes, toothache, and hypertension. Among these 150 are about 20 different compounds that have antineoplastic activity. Vincristine and vinblastine are pharmaceuticals derived from compounds in the periwinkle plant and are among the most commonly used vinca alkaloid derivatives in medicine. They are typically used as part of a chemotherapy regimen for various cancers. The two chemotherapeutics are administered intravenously and should never be administered intrathecally. Intrathecal administration of vinblastine or vincristine is always the result of an error, is a neurosurgical emergency, and is associated with life-threatening complications (Special Considerations: SC7 and SC8). There are a few case reports of intramuscular administration of these antineoplastics, but they will not be discussed because there are so few, and readers are referred to the actual publications for further information. Although other vinca derivatives exist, some have oral formulations and share similar modes of action (causing microtubule dysfunction); however, this section focuses primarily on vincristine and vinblastine. Regardless, the pathophysiology of disease, clinical manifestations of illness, and management of poisoning from similar compounds and the plant itself are similar to those of vincristine and vinblastine.

Pathophysiology

Vincristine and vinblastine are used specifically for the treatment of patients with leukemias, lymphomas, and certain solid tumors. Their mechanism of activity is similar to the mechanisms of activity of colchicine, podophyllotoxin, and the taxoids (eg, paclitaxel, docetaxel). These chemotherapeutics disrupt microtubule assembly from tubulin subunits by either preventing their formation or depolymerization, both of which are necessary for routine cell maintenance. Vinblastine binds to the β-subunit of the tubulin heterodimer at a specific region known as the vinblastine binding site. Microtubules are responsible for
several basic cellular functions, including cell division, axonal transport of nutrients and organelles, and cellular movement. Mitotic metaphase arrest is commonly observed because of the inability to form spindle fibers from the microtubules. Cell death quickly ensues as a result of the interruption of these homeostatic functions, accounting for the clinical manifestations.

The mechanism of neurotoxicity is not well understood but is related to inhibition of microtubular synthesis, which leads to axonal degeneration in the peripheral nervous system. A brain biopsy of a patient with a vincristine-related death showed neurotubular dissociation, which is characteristic of vincristine damage in experimental animals.

A single study demonstrated in mice poisoned with a vinca derivative that administration of murine monoclonal antibodies active against vinca alkaloids is protective and significantly improved survival.

Genetic polymorphisms are associated with the development of vincristine-associated neuropathy. A mutation in the CEP72 gene, which encodes for a protein involved in microtubule formation, and reduced expression of the genes that encode for CYP3A5 are associated with vincristine-induced peripheral neuropathy.

Pharmacokinetics

After IV administration, vincristine is rapidly distributed to tissue stores and highly bound to proteins and RBCs. The capacity of vincristine to be bound by plasma proteins ranges from 50% to 80%. In more than 50% of children given IV vincristine, serum concentrations were not detected 4 hours after administration. The vinca alkaloids are primarily eliminated through the liver. Patients with hepatic dysfunction are susceptible to toxicity. Elimination of vincristine occurs via the hepatobiliary system, and it has a terminal plasma half-life of about 24 hours. Vincristine overdose is the most frequently reported antineoplastic overdose in the literature. This is because there are at least four different potential inappropriate ways to dose and administer vincristine, including confusing it with vinblastine, misinterpreting the dose, administering it by the wrong route, and confusing two different-strength vials. The normal dose of vincristine is 0.06 mg/kg, and a single dose should not exceed 2 mg for either an adult or child.

Drug Interactions

Administration of itraconazole with therapeutic doses of intravenously administered vincristine cause toxicity because of at least two primary reasons: (1) itraconazole-induced inhibition of certain cytochrome P450 enzymes (most likely the CYP3A subfamily) delays vincristine metabolism in vivo, and (2) inhibition of P-gp–mediated efflux of vincristine from inside cells, where it then accumulates. Coadministration of other azole antifungals, cyclosporine, isoniazid, erythromycin, mitomycin C, phenytoin, and nifedipine are also implicated in vincristine toxicity for the same aforementioned reasons. Azole antifungals exacerbate vinblastine-related hyponatremia in children.
**Toxic Dose**

The minimum toxic doses associated with adverse health effects from a single dose of vincristine and vinblastine are not well established. However, chemotherapeutic regimens tend to keep single doses at or below 2 mg to decrease the likelihood of peripheral neuropathy. Unfortunately, toxicity occurs with cumulative dosing over time, as that typically occurs with chemotherapeutic regimens. Peripheral neuropathy tends to begin after a cumulative dose (administered over multiple sessions, not all at once) of 30 to 40 mg.\(^{24}\)

**Clinical Presentation**

Despite their similarity in structure, vincristine and vinblastine differ in their clinical toxicity. Vincristine produces less bone marrow suppression and more neurotoxicity than does vinblastine. During the therapeutic use of vincristine, myelosuppression occurs in only 5% to 10% of patients.\(^ {105}\) However, this effect is common in the overdose setting, and when it occurs, the need for replacement blood products and concern for overwhelming infection is apparent.\(^ {130}\) The decrease in cell counts begins within the first week and lasts for up to 3 weeks. Other manifestations of acute vincristine toxicity are mucositis, central nervous system disorders, and syndrome of inappropriate antidiuretic hormone (SIADH).

Central nervous system disorders are varied and unusual during therapeutic vincristine therapy because of its poor penetrance of the blood-brain barrier. They are, however, more common when there is delayed elimination, damage to the blood brain-barrier, overdose, or inadvertent intrathecal administration. Generalized seizures from toxicity or secondary effects generally occur from 1 to 7 days after exposure.\(^ {109,115,120,197}\) Other manifestations are depression, agitation, insomnia, and hallucinations. Vincristine stimulation of the hypothalamus appears to be responsible for the fevers and SIADH noted in overdosed patients.\(^ {177}\) The fevers begin 24 hours after exposure and last 6 to 96 hours. Serum electrolytes need to be monitored, typically for 10 days.

Autonomic dysfunction is observed, and it commonly includes ileus, constipation, and abdominal pain. Paraparesis, paraplegia, atony of the bladder, cranial nerve palsies (specifically ptosis) hypertension, and hypotension also occur.\(^ {67,73,120,227}\)

Ascending peripheral neuropathies occur after inadvertent large ingestions and during routine chemotherapy. The risk is limited somewhat by keeping the total for a single dose below 2 mg.\(^ {191}\) Neuropathy appears after an overdose, starting at about 2 weeks and lasting for 6 to 7 weeks. Paresthesias, neuritic pain, ataxia, bone pain, wrist drop, foot drop, involvement of cranial nerves III to VII and X, and diminished reflexes are observed.\(^ {217}\) Cranial nerve III involvement, manifesting as bilateral ptosis, was reported in several cases of vincristine toxicity in children.\(^ {100,162}\) The incidence of paresthesia increases with dose and is reported to be 56% in patients treated at doses between 12.5 and 25 mcg/kg.\(^ {105}\) At a dose of 75 mcg/kg, the incidence of patients with a sensory disorder increased by sixfold. The loss of reflexes, the
earliest and most consistent sign of vincristine neuropathy, is maximal at 17 days after a single massive dose. Muscular weakness is a limiting point in therapy and typically involves the distal dorsiflexors of the extremities, although laryngeal involvement is also reported. These severe neurologic symptoms may be reversed by either withholding therapy or reducing the dosage upon manifestation of these findings. Unlike the vinca alkaloids, Taxol-induced peripheral neuropathy is predominantly sensory and resolves faster with discontinuation. This is because of the different effects on microtubule assembly by these xenobiotics.

Vincristine-induced myocardial infarctions are reported, but their cause is not understood. Although rare, vincristine administration is associated with an allergic-type cutaneous reaction.

Testing

Vincristine and vinblastine testing is not readily available at most hospitals. Organ-specific toxicity is evaluated through the use of routinely available laboratory tests (eg, cell blood count, electrolytes, renal and liver function tests).

Management

Generalized seizures are a life-threatening complication of vincristine or vinblastine overdose. Treatment with benzodiazepines is usually successful and is the recommended front-line antiepileptic intervention, although phenytoin was used successfully in a patient with barbiturate hypersensitivity. Prophylactic phenobarbital and benzodiazepines were used to prevent seizures in two patients. Supportive and symptomatic care is recommended for organ specific toxicity as needed. Monitoring daily blood counts is recommended daily, and G-CSF is used to treat neutropenia. Of note is that the RBC response from the use of erythropoietin is limited because of the induction of metaphase arrest in the erythroblasts.

The symptoms of acute toxicity usually last for 3 to 7 days, and the neurologic sequelae lasts for months. Nerve conduction studies are helpful in assessing the extent of any clinical signs and symptoms of peripheral neuropathy.

Clinical findings of a peripheral neuropathy appears after an excessive dose or after multiple small doses in which the cumulative dose exceeds 30 to 40 mg. Treatment for this condition is variable and includes pain and paresthesia management, including opioids, nonsteroidal antiinflammatory drugs, tricyclic antidepressants, vitamin E, gabapentin, and lamotrigine. In a controlled clinical trial for vincristine-induced peripheral neuropathy, glutamic acid therapy had limited efficacy. Patients receiving vincristine therapy were given glutamic acid as 500 mg orally 3 times a day. There was a decreased incidence in loss of the Achilles tendon reflex and a delayed onset of paresthesias in the glutamic acid–treated group. No reported adverse effects with glutamic acid were observed in this investigation. Animal studies involving the administration of glutamic and aspartic acid to mice poisoned with either vinblastine or vincristine.
demonstrate increased survival and decreased sensorimotor peripheral neuropathy.\textsuperscript{33,60,112} The mechanisms of these observed effects with glutamic acid remain unclear, but several authors have suggested the ability of glutamic acid to competitively inhibit a common cellular transport mechanism for vincristine,\textsuperscript{29,58} its ability to assist in the stabilization of tubulin and promote its polymerization into microtubules,\textsuperscript{35,96} and the ability of glutamic acid to improve cellular metabolism by overcoming the inhibition in the tricarboxylic acid cycle.\textsuperscript{72,114} Although the role of glutamic acid in acute toxicity needs further study, it is not harmful and is reasonable to try in this setting. Glutamic acid is given as 500 mg orally three times a day and continued until the serum \textit{vincristine} concentration is below toxicity.\textsuperscript{113} L-Glutamic acid is the preferred stereoisomer because it is biologically active, and this product is available as a powder from various distributors in the United States. Case reports document success in treating bilateral ptosis with combinations of \textit{pyridoxine} and pyridostigmine\textsuperscript{162} or \textit{pyridoxine} and thiamine.\textsuperscript{100} These therapies are also reasonable to institute.

Leucovorin shortens the course of vincristine-induced peripheral neuropathy\textsuperscript{92} and myelosuppression.\textsuperscript{122} The mechanism is attributed to the ability of leucovorin to overcome a vincristine-mediated block of dihydrofolate reductase and thymidine synthetase (Antidotes in Depth: A12).\textsuperscript{92} However, neither leucovorin\textsuperscript{18,111,206} nor pyridoxine\textsuperscript{111} was definitely shown to be effective. Therefore, there is insufficient evidence from which to make a recommendation regarding its use as a therapy at this time. An initial experimental investigation evaluating the efficacy of antibody therapy to limit vinca alkaloid toxicity shows promise.\textsuperscript{93} Unfortunately, vinca alkaloid specific antibodies for human poisoning are not commercially available.

The rapid distribution and high protein binding characteristics of \textit{vincristine} favor early intervention and methods other than hemodialysis. Double-volume exchange transfusion was performed at 6 hours postexposure in three children who were overdosed with 7.5 mg/m\textsuperscript{2} of IV vincristine.\textsuperscript{122} This procedure replaced approximately 90\% of the circulating blood volume by exchanging twice the patient’s blood volume. Of the two survivors, their respective postexchange serum \textit{vincristine} concentrations were 57\% and 71\% lower than their preexchange concentrations. The amount of \textit{vincristine} removed was not determined. Although these patients developed peripheral neuropathies, myelosuppression, and autonomic instability, the author noted that the duration of illness was shorter than previously reported. Thus, based on the pharmacokinetic profile of \textit{vincristine} and these two reports, exchange transfusion in children is the preferred method of enhanced elimination when the patient presents soon after the administration of the drug, and plasmapheresis is the preferred method in adults.

Plasmapheresis was attempted with vinca alkaloid overdoses.\textsuperscript{130,169} In an 18-year-old patient who received two 8-mg IV doses of \textit{vincristine} at 12-hour intervals, the procedure was performed 6 hours after the second dose, and 1.5 times the plasma volume was plasmapheresed.\textsuperscript{169} Postplasmapheresis serum \textit{vincristine} concentration was 23\% lower than the starting concentration. The patient survived with myelosuppression, neurotoxicity, and SIADH.
One case of IV vinblastine overdose was reported to be successfully managed with plasma exchange procedures performed at 4 hours and 18 hours after vinblastine administration, resulting in markedly less toxicity than what was expected.\textsuperscript{195}

Patients receiving an overdose of vincristine intravenously should be admitted to a cardiac-monitored bed and observed for 24 to 72 hours.\textsuperscript{133} If patients remain asymptomatic during the observation period, they can be discharged with follow-up for bone marrow suppression and SIADH; otherwise, depending on the patient’s clinical condition, continual observation for progression of neurologic symptoms is warranted.\textsuperscript{22}

**SUMMARY**

Colchicine toxicity is evident several hours after ingestion and consists of severe nausea, vomiting, diarrhea, and abdominal pain followed by pancytopenia several days later. Colchicine-poisoned patients have a higher risk of sudden cardiac death, especially during the period between 24 and 36 hours after ingestion; increasing serial troponin concentrations in these patients suggest a higher risk of cardiovascular complications. Podophyllum toxicity is less pronounced compared with colchicine and occurs after dermal application (Table 34–2).
### TABLE 34–2

**Comparison of Antimitotic Overdose**

<table>
<thead>
<tr>
<th></th>
<th>Colchicine</th>
<th>Podophyllum Resin</th>
<th>Vincristine</th>
<th>Vinblastine</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Route of exposure</strong></td>
<td>PO</td>
<td>PO and cutaneous</td>
<td>IV</td>
<td>IV</td>
</tr>
<tr>
<td><strong>Initial symptoms</strong></td>
<td>GI effects,(^a) neurologic effects (obtundation, confusion, delirium, seizures, myoneuropathy, areflexia)</td>
<td>GI effects,(^a) fever, neurologic effects (obtundation, confusion, delirium, paresthesias, lost reflexes, cranial nerve involvement)</td>
<td>GI effects,(^a) fever, neurologic effects (depression, agitation, delirium, paresthesias, muscle weakness, lost reflexes, cranial nerve involvement)</td>
<td>GI effects,(^a) fever, myalgias, neurologic effects (but less than vincristine)</td>
</tr>
<tr>
<td><strong>Initial symptom onset</strong></td>
<td>Several hours after ingestion; delayed onset beyond 12 h very unlikely</td>
<td>Several hours after ingestion; delayed presentation (past 12 h) is possible, especially after cutaneous exposure</td>
<td>Usually within 24–48 h</td>
<td>Usually within 24–48 h</td>
</tr>
<tr>
<td><strong>Hematologic effects</strong></td>
<td>Leukocytosis (24–48 h after ingestion); pancytopenia (beginning 48–72 h after ingestion)</td>
<td>Similar to colchicine; however, not well characterized and reported less frequently</td>
<td>Occurs but decreased severity compared with vinblastine</td>
<td>Myelosuppression; increased severity compared with vincristine</td>
</tr>
<tr>
<td></td>
<td>Colchicine</td>
<td>Podophyllum Resin</td>
<td>Vincristine</td>
<td>Vinblastine</td>
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<td>---------------------</td>
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<tr>
<td>CNS effects</td>
<td>Late (48–72 h after ingestion); obtundation, confusion, and lethargy secondary to progression of MSD</td>
<td>Can be early (&lt;12 h after ingestion); typically occur later or secondary to progression of MSD</td>
<td>Variable; cranial neuropathies; seizures; obtundation, confusion, and lethargy; also occur because of progression of MSD</td>
<td>Occurs but <em>decreased severity</em> compared with vincristine</td>
</tr>
<tr>
<td>Delayed PNS effects</td>
<td>Myoneuropathy most common (can also occur early); reported most often in chronic colchicine users with kidney dysfunction</td>
<td>Peripheral sensorimotor axonopathy</td>
<td>Autonomic and ascending peripheral neuropathy; <em>increased severity</em> compared with vinblastine</td>
<td>Autonomic and peripheral neuropathy; <em>decreased severity</em> compared with vincristine</td>
</tr>
<tr>
<td>Clinical course</td>
<td>Recovery or MSD and death</td>
<td>Recovery or MSD and death</td>
<td>Recovery or MSD and death; SIADH</td>
<td>Recovery or MSD and death; SIADH</td>
</tr>
<tr>
<td>Management</td>
<td>Supportive; GI decontamination (activated charcoal, orogastric lavage for life-threatening ingestions if within 1–2 h, no contraindications present, and provider is proficient in the procedure); G-CSF for neutropenia</td>
<td>Supportive; GI decontamination (activated charcoal) for oral exposures and skin decontamination for cutaneous exposures</td>
<td>Primarily supportive; G-CSF for neutropenia For treatment of intrathecal overdoses, see Special Considerations: SC7</td>
<td>Primarily supportive; G-CSF for neutropenia; exchange transfusion, plasmapheresis or plasma exchange are reasonable for severe toxicity For treatment of intrathecal overdoses, see Special Considerations: SC7</td>
</tr>
</tbody>
</table>
Nausea, vomiting, diarrhea, and abdominal discomfort.

CNS = central nervous system; G-CSF = granulocyte-colony stimulating factor; GI = gastrointestinal; IV = intravenous; MSD = multisystem organ dysfunction; PNS = peripheral nervous system; PO = oral; SIADH = syndrome of inappropriate antidiuretic hormone secretion.

Early GI decontamination and supportive treatment are the hallmarks of therapy for all colchicine and podophyllin exposure because there are no commercially available and proven antidotes.

Excessive doses of intravenously administered vincristine or vinblastine cause severe toxicity and are managed with supportive and symptomatic care as well. Although definitive data confirming clinical benefit is lacking, exchange transfusion, plasmapheresis, and plasma exchange are reasonable in severely poisoned patients as soon as possible; any potential efficacy likely decreases as the interval from exposure to treatment initiation increases.

Disclaimer

The findings and conclusions in this article are those of the authors and do not necessarily represent the views of the Centers for Disease Control and Prevention or the Agency for Toxic Substances and Disease Registry.

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