Colchicine - an overview | ScienceDirect Topics

Colchicine

Swetaleena Dash, in Reference Module in Biomedical Sciences, 2023

Abstract

Colchicine is primarily used in the treatment of acute gouty arthritis. It is also used to treat Behcet's disease, pericarditis and familial Mediterranean fever. It is available as a pharmaceutical preparation and also found in plants in particular the autumn crocus (*colchicum autumnale*). Colchicine binds to tubulin and prevents its polymerization into microtubules, subsequently disrupting microtubule function. Colchicine has a narrow therapeutic index with risk of toxicity occurring at doses close to the therapeutic range. Gastrointestinal side effects are common at high doses. Low blood cell counts and rhabdomyolysis are more severe side effects of colchicine. Colchicine toxicity has been divided into three stages: a gastrointestinal phase, the multiorgan failure phase, and if the patient survives, the recovery phase, with a risk of sepsis. Treatment of colchicine toxicity is largely supportive.

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URL: https://www.sciencedirect.com/science/article/pii/B978012824315200498X

Colchicine

In Meyler's Side Effects of Drugs (Sixteenth Edition), 2016

Musculoskeletal

Acute rhabdomyolysis with fever, muscle cramps, rises in creatine phosphokinase and lactic acid dehydrogenase activity, phlebitis at the injection site, and transitory leukopenia and thrombocytopenia have been reported [17].

Colchicine-induced myopathy generally causes painless subacute muscle weakness but can cause pain [18].

- A 76-year-old man with chronic renal failure and gout who was taking colchicine 0.5 mg tds for 3 days each month developed bilateral lower leg weakness and severe myalgia. His serum creatinine concentration was 681 μmol/l and creatinine kinase 959 IU/l. There were reduced amplitudes of motor and sensory nerve conduction velocities and electromyography showed small-amplitude, short-duration, polyphasic waves over the right biceps. A muscle biopsy showed vacuolar changes in the cytoplasm, all consistent with colchicine neuromyopathy. After withdrawal of colchicine, the creatinine kinase activity fell by about 50% in 6 days, the myalgia abated, and the muscle weakness improved gradually over the next 2 weeks.

Colchicine-induced myopathy with associated myotonia has rarely been reported [19]. Colchicine myopathy with or without neuropathy can occur more often than has previously been thought, especially in elderly patients with chronic renal insufficiency taking long-term low doses of colchicine [20–22]. Acute rhabdomyolysis can occur (see also **Drug-drug interactions** below).

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Colchicine

H.A. Spiller, in Encyclopedia of Toxicology (Third Edition), 2014

Toxicokinetics

Colchicine is readily absorbed from the gastrointestinal tract. In therapeutic dosing, peak serum levels occur in 30–120 min. Colchicine undergoes deacetylation and hydrolysis in the liver. It has a rapid initial distribution phase, with a plasma half-life of 19 or 20 min, suggesting swift uptake by the tissues. The volume of distribution is 2.2 l kg^{-1}. Up to 40% of colchicine is excreted in the urine, with 20–30% of this as unchanged drug. The majority of the drug undergoes enterohepatic recirculation and is excreted via bile and feces. The average elimination half-life is 20 h.

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Colchicine

Mark G. Papich DVM, MS, DACVCP, in Papich Handbook of Veterinary Drugs (Fifth Edition), 2021

Indications and Clinical Uses

In people, colchicine is used to treat gout. In animals, it has been used as an antifibrotic agent to decrease fibrosis and development of hepatic failure (possibly by inhibiting formation of collagen). However, the efficacy for controlling liver fibrosis in chronic liver disease is questionable and unproven. Anti-inflammatory effects may be caused by inhibition of neutrophil and mononuclear migration. Antifibrotic effects result from blockage of microtubular-mediated transcellular movement of proteins and to inhibit secretion of procollagen molecules into the extracellular matrix. It has also been used in animals to control amyloidosis. In Shar-Pei dogs, colchicine has been used to treat a fever syndrome, possibly because of its use in people for treating Mediterranean fever.

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Hepatobiliary Cytoprotective Agents

Cynthia R.L. Webster, in Canine and Feline Gastroenterology, 2013

Colchicine

Colchicine is a microtubular inhibitor that is used in hepatobiliary disease primarily for its antifibrotic effects. Colchicine's main mechanism of action is to inhibit collagen secretion, but it can also suppress inflammation by inhibiting neutrophil migration and degranulation and promote collagen degradation by stimulating collagenase activity. In isolated case reports, colchicine has shown variable efficacy in canine chronic hepatitis when used at 0.01 to 0.3 mg/kg/day PO.[34,35] In human medicine, metaanalysis of several large, randomized clinical trials of patients with chronic hepatitis/cirrhosis have not shown a beneficial effect of colchicines, and some studies actually have shown

increased morbidity/mortality in the colchicine-treated patients.[36] Colchicine use should be limited to those canine patients with noninflammatory fibrotic hepatopathies. The major side effect is hemorrhagic diarrhea, although bone marrow suppression and peripheral neuropathies have been reported in humans. The use of colchicine has not been reported in cats.

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Systemic autoinflammatory syndromes

Jeroen C.H. van der Hilst, ... Anna Simon, in Clinical Immunology (Fourth Edition), 2013

Colchicine

Colchicine is the treatment of choice in FMF.[10] It is highly effective in preventing attacks. In fact, it is so effective in preventing attacks that response to colchicine has been used as a clinical criterion for diagnosing FMF. The mechanism of action is unknown. Colchicine therapy is also very efficient in preventing amyloidosis. Therefore, all patients with FMF should receive colchicine, regardless of the severity and frequency of attacks. In patients who already have amyloidosis, intensive treatment can sometimes arrest progression or even partially reverse the process.

The average daily dose is 1–1.5 mg. In cases in which this is not sufficient to prevent attacks the dose can be increased to up to 3 mg.

There is a small subset of patients who do not respond to colchicine.

The most commonly encountered side effect of colchicine treatment, gastrointestinal discomfort with diarrhea, usually resolves with dose reduction. Myopathy, neuropathy, and leukopenia are rare, but serious, side effects that primarily occur in patients with renal or liver impairment or because of interaction with co-medication.

In animal studies teratogenic effects are only seen at extremely high dosages. The potential teratogenic role of colchicine arises from its effect on microtubules, and there has been some concern that colchicine could therefore increase inborn errors, especially

trisomy. However, multiple studies show that colchicine is safe to use during pregnancy, and can also be used while breastfeeding.[37,38] In therapeutic dosages colchicine does not interfere with sperm quantity or quality. Furthermore, a clinical series of male patients on colchicine did not detect a negative effect on fertility.

There is generally no place for colchicine in the treatment of autoinflammatory syndromes other than FMF, although some patients with a suspected autoinflammatory syndrome of unknown origin will have some favorable effect.

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Anti-inflammatory and antipyretic analgesics and drugs used in gout

J.K. Aronson, in Side Effects of Drugs Annual, 2009

Colchicine *(SEDA-15, 883; SEDA-28, 133; SEDA-29, 125; SEDA-30, 133)*

Nervous system

Colchicine-induced *neuromyopathy* generally causes painless subacute muscle weakness but can cause pain (187[A]).

- A 76-year-old man with chronic renal failure and gout who was taking colchicine 0.5 mg tds for 3 days each month developed bilateral lower leg weakness and severe myalgia. His serum creatinine concentration was 681 μmol/l and creatinine kinase 959 IU/l. There were reduced amplitudes of motor and sensory nerve conduction velocities and electromyography showed small-amplitude, short-duration, polyphasic waves over the right biceps. A muscle biopsy showed vacuolar changes in the cytoplasm, all consistent with colchicine neuromyopathy. After withdrawal of colchicine, the creatinine kinase activity fell by about 50% in 6 days, the myalgia abated, and the muscle weakness improved gradually over the next 2 weeks.

Psychological

Despite that fact that studies in animals have suggested that colchicine may adversely affect cognitive function, in 55 patients, mean age 74 years, with familial Mediterranean fever colchicine for an average of 25 years had no adverse effects on cognitive function (188c).

Skin

Colchicine toxicity in a patient presenting with altered mental function caused a diffuse, blanchable, violaceous, morbilliform rash on the trunk and proximal limbs; metaphase-arrested keratinocytes with underlying basal vacuolization were typical of colchicine toxicity (189[A]).

Drug–drug interactions

The pharmacokinetics and drug interactions of colchicine have been reviewed (190[R]). Three proteins are important:

- tubulin, the pharmacological receptor (target) for colchicine; colchicine binds to tubulin, preventing polymerization and thereby disrupting microtubule function; the dissociation half-life of the tubulin–colchicine complex is 20–30 hours and this determines the half-life of colchicine;
- intestinal and hepatic CYP3A4, by which colchicine is metabolized; drug interactions can occur when colchicine is combined with other drugs that are CYP3A4 substrates;
- P-glycoprotein, which affects its tissue distribution and excretion via the biliary tract and kidneys; drug interactions can occur when colchicine is combined with other drugs that are P-glycoprotein substrates.

Clarithromycin

An interaction of colchicine with clarithromycin (SEDA-30, 133) has again been reported (191[A]).

Statins

Interactions of colchicine with statins (SEDA-30, 134) have again been reported, resulting in rhabdomyolysis.

- A 74-year-old Asian man who was taking prophylactic colchicine for gout developed proximal muscle weakness 2 weeks after starting to take lovastatin (192[A]). The deep tendon reflexes were symmetrical and reduced in both arms and legs. Serum creatine kinase was 8370 U/l (0–130 U/l), and electromyography showed a myopathic pattern. Lovastatin and colchicine were withdrawn and after several weeks the creatine kinase activity gradually returned to normal, with normal muscle strength.
- A 45-year-old man with nephrotic syndrome took colchicine 1.5 mg/day for amyloidosis for 3 years without adverse effects (193[A]). He then took atorvastatin 10 mg/day for hypercholesterolemia and after 2 weeks developed dyspnea, altered thinking, severe fatigue, myalgia, and reduced muscle strength. The creatinine concentration was 714 μmol/l, the creatine kinase activity 9035 U/l, and there was myoglobinuria and acute renal failure. His muscle strength improved after withdrawal of atorvastatin and colchicine.

Effects on CYP3A4 and P glycoprotein were presumably at least partly responsible for these interactions.

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Ghrelin

Haruaki Kageyama, ... Seiji Shioda, in Methods in Enzymology, 2012

2.1 Colchicine treatment

Colchicine treatment enhances the ghrelin immunoreaction. Colchicine is a tubulin polymerization inhibitor and is known to inhibit cytoplasmic transport and exocytosis (Thyberg and Moskalewski, 1985). Hence, treatment of animals with colchicine is commonly used to promote the accumulation of secretory proteins in the cytoplasm.

1. Deeply anesthetize rat with sodium pentobarbital (40 mg/kg, intraperitoneal injection) and inject colchicine (200 μg/5 μl saline) into the lateral ventricle (0.8 mm posterior to bregma; 1.3 mm lateral from the midline; and 3.5 mm below the outer surface of the skull, according to the Paxinos and Watson atlas of rat brain (Paxinos and Watson, 1986)).

2. Forty-eight hours later, confirm tetraplegia of the colchicine-treated rat.

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Electrophysiologic Techniques in the Evaluation of Patients with Suspected Neurotoxic Disorders

Michael J. Aminoff, James W. Albers, in Aminoff's Electrodiagnosis in Clinical Neurology (Sixth Edition), 2012

Colchicine

Colchicine is a potential cause of a myopathy–neuropathy syndrome.[71] Colchicine myopathy is associated with an elevated serum creatine kinase level. Rhabdomyolysis may occur with sufficient myoglobinuria to produce acute renal failure, typically in association with multiple risk factors in addition to colchicine.[72] The needle EMG examination in colchicine myopathy is reported to show proximal muscle abnormalities characterized by profuse fibrillation potentials and positive waves, complex repetitive discharges, and "myopathic" motor unit potentials.[73] In muscle biopsies, the presence of

a vacuolar myopathy with acid phosphatase-positive vacuoles, myofibrillar disarray foci, and degenerating and regenerating muscle fibers, without evidence of inflammation, vasculitis, or connective tissue disease, has been documented.[74] The mechanism by which colchicine produces myopathy is thought to involve membrane disruption and segmental necrosis of muscle fibers. The myopathy improves, sometimes dramatically, shortly after discontinuation of the colchicine.[75]

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Manipulation of Ploidy Level☆

L. Crespel, J. Meynet, in Reference Module in Life Sciences, 2017

Mitotic Polyploidization

Mitotic polyploidization consists in doubling the somatic chromosome number using chemicals with antimitotic activity such as colchicines.

Colchicine has been used for doubling the number of chromosomes of many crop plants over a period of more than 50 years. This alkaloid, obtained from the wild *Colchicum autumnale*, blocks the cell at metaphase of mitosis. It binds to one tubulin end and prevents its polymerization and causes disappearance of the mitotic spindle.

Other chemicals with antimitotic activity similar to colchicine such as colcemid, or more recently oryzalin, were equally used. Oryzalin inhibits spindle formation at approximately one thousandth of the concentration of colchicine. It was preferred to colchicine because it is safer to use, cheaper to apply and less likely to cause chromosome aberrations in plant tissues.

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