REVIEW

THE AMERICAN JOURNAL of MEDICINE®

Colchicine: Old and New

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ABSTRACT

Although colchicine has been a focus of research, debate, and controversy for thousands of years, the US Food and Drug Administration just approved it in 2009. Over the past decade, advances in the knowledge of colchicine pharmacology, drug safety, and mechanisms of action have led to changes in colchicine dosing and to potential new uses for this very old drug. In this review, we discuss the pharmacologic properties of colchicine and summarize what is currently known about its mechanisms of action. We then discuss and update the use of colchicine in a variety of illnesses, including rheumatic and, most recently, cardiovascular diseases.

Published by Elsevier Inc. • The American Journal of Medicine (2015) 128, 461-470

KEYWORDS: Cardiovascular disease; Colchicine; Gout; Inflammation

Although colchicine's medicinal properties have been recognized for centuries, the drug was first approved in 2009, under the US Food and Drug Administration (FDA) unapproved drugs initiative.[1] FDA approval brought changes in colchicine dosing regimens, and a greater emphasis on safety in the context of comorbidities and drug–drug interactions. Even before FDA approval, investigations had begun to widen colchicine's range of clinical use, from gout and familial Mediterranean fever to a variety of rheumatologic and cardiovascular applications (**Table**).[2-25] Here we review colchicine's basic biology and classical uses, and provide an update on newer and potential uses in diseases with inflammatory etiologies.

Funding: None.

Conflict of Interest: AS: None. SK: None. MHP is the recipient of an investigator-initiated grant and also serves as a study site investigator for a trial supported by Takeda, Inc.; is the recipient of an investigator-initiated grant from Savient, Inc.; is the recipient of an investigator-initiated grant and has served as a consultant for Crealta, Inc.; and has served as a consultant for Astra-Zeneca, Inc. BS is the recipient of an investigator-initiated grant (drug and placebo only) from Takeda, Inc.

Authorship: All authors participated in all aspects of this manuscript, including conception, research, writing, and editing.

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0002-9343/$ -see front matter Published by Elsevier Inc.
http://dx.doi.org/10.1016/j.amjmed.2014.12.010

PHARMACOLOGIC PROPERTIES

Colchicine is a tricyclic, lipid-soluble alkaloid with a long terminal half-life (20 to 40 hours) and bioavailability ranging from 24% to 88% (**Figure 1**). Within the bloodstream, ~40% of colchicine binds to albumin.[26] Although peak plasma concentrations occur 1 hour after administration, maximal anti-inflammatory effects develop over 24 to 48 hours, based on intraleukocyte accumulation.[27] Colchicine reaches much higher concentrations within leukocytes than in plasma, and persists there for several days after ingestion,[2,3] with concentrations ranging from 4 to 64 ng/10^9.[28]

Colchicine preferentially binds 3 proteins: tubulin, cytochrome P3A4 (CYP3A4), and P-glycoprotein. The dissociation half-life of colchicine from tubulin is 20-40 hours, which primarily defines colchicine's long clinical half-life.[29] Colchicine's persistence on tubulin prevents the fusion of autophagic vacuoles with lysosomes in neuronal, marrow, and muscle cells, resulting in risk of damage to these organ systems,[30] particularly for patients with hepatic or renal impairment.[31,32]

CYP3A4 and P-glycoprotein are largely responsible for colchicine metabolism (**Figure 2**). CYP3A4 is found in hepatocytes and enterocytes, and metabolizes colchicine to 2- and 3-demethylcolchicine. P-glycoprotein is an ATPase efflux pump found in enterocytes, hepatocytes, renal cells, and the blood–brain barrier; it extrudes colchicine from the

gastrointestinal tract to limit gastrointestinal absorption. Together with renal excretion, these systems determine overall colchicine serum levels. Individuals vary in their levels of expression of CYP3A4 and P-glycoprotein; lack of adequate response to colchicine in certain patients may relate to over-expression of one or both of these proteins.[29]

CYP3A4 and P-glycoprotein are also largely responsible for colchicine's numerous drug-drug interactions, as each interacts with a range of other drugs. Because of CYP3A4 interactions, colchicine metabolism is impaired in patients taking clarithromycin, fluoxetine, paroxetine, nefazodone, indinavir and other protease inhibitors, tolbutamide and azole antifungals, cimetidine, and several non-dihydropyridine calcium channel blockers, each of which is metabolized through this pathway.[33] Fatalities have been reported with unadjusted co-administration of colchicine and clarithromycin.[34,35] Drugs that are eliminated by the enterocyte P-glycoprotein transporter include macrolides, protease inhibitors, chemotherapeutic agents, glucocorticoids, calcium channel blockers, and certain statins.[33] Colchicine particularly interacts with cyclosporine because of P-glycoprotein interaction with both of these medications.[36] Dose adjustment of colchicine in the setting of many of the aforementioned agents is mandated and described in detail in the manufacturer's prescribing information.[37]

Bioavailability of colchicine in the elderly is comparable with that in younger adults. However, colchicine's volume of distribution and total body clearance are significantly reduced, leading to a higher plasma concentration and a significantly greater risk of toxicity.[38] To counter this effect, some experts recommend reducing the colchicine dose by up to 50% in patients who are older than 70 years of age.[39]

CLINICAL SIGNIFICANCE

- Colchicine is considered first-line therapy for treatment of acute gout, prophylaxis of gout, and familial Mediterranean fever. It is also commonly used in other diseases, including pseudogout, pericarditis, Behçet's disease, and neutrophilic dermatoses.
- Colchicine's anti-inflammatory properties may be beneficial in treating or preventing cardiovascular disease, including pericarditis, postsurgical atrial fibrillation, and acute cardiovascular syndromes.

MECHANISMS OF ACTION

Colchicine binds to free tubulin dimers, which, when incorporated into nascent microtubules, disrupt further microtubule polymerization. Abrogation of microtubule polymerization inhibits vesicle transport, cytokine secretion, phagocytosis, migration, and division. At higher concentrations, colchicine may also induce some microtubule dissociation.[39]

In neutrophils, colchicine inhibits intracellular signaling molecules including tyrosine kinases and phospholipases, and inhibits chemotaxis and lysosomal enzyme release during phagocytosis.[40] Recent studies suggest that colchicine also modulates neutrophil deformability to suppress neutrophil extravasation.[41] In addition, colchicine inhibits neutrophil superoxide anion production and increases leukocyte cAMP, which is known to suppress neutrophil function.[42]

At low concentrations (eg, 3 nM), colchicine modulates the distribution of E-selectin adhesion molecules on endothelial cells, inhibiting neutrophil adhesion to, and extravasation from, the vasculature. At higher concentrations (eg, 300 nM), colchicine reduces L-selectin expression on neutrophils, further impeding neutrophil-endothelial cell adhesion. These concentration-dependent effects may partly explain the observation that low doses (eg, 0.6 mg/day) of colchicine may prevent, but doses higher (eg, $\geq$1.8 mg) are needed to suppress acute gouty attacks.[43]

Recently, colchicine has been shown to suppress the activation of caspase-1, the enzymatic component of the nucleotide-binding oligomerization domain receptor (NOD-like receptor) family pyrin 3 (NLRP3) inflammasome. Caspase-1 suppression blocks conversion of pro-interleukin (IL)-1β to active IL-1β, leading to secondary reductions in cytokines such as tumor necrosis factor-alpha (TNF-α) and IL-6. Colchicine's effect on this process may be upstream of, rather than directly on, the inflammasome.[44] To date, inflammasome inhibition has been assessed at colchicine concentrations 10- to 100-fold higher than those achieved in serum.[33] Whether colchicine inhibits caspase-1 at physiologic concentrations, or whether colchicine accumulation in leukocytes is sufficient to block the inflammasome, remains to be determined.

Other potential anti-inflammatory activities include modulation of pyrin expression (see familial Mediterranean fever section), downregulation of lipopolysaccharide-induced TNF-α mRNA production, inhibition of histamine release by mast cells, suppression of procollagen synthesis, and promotion of collagenase activity.[45-47]

COLCHICINE TOXICITY

The commonest side effects of colchicine are gastrointestinal, with nausea, vomiting, and particularly diarrhea occurring in 5%-10% of patients, even at recommended doses. Dose reduction may permit resolution of these symptoms. Colchicine doses of 0.5 to 0.8 mg/kg are highly toxic, and doses of more than 0.8 mg/kg are typically lethal; to reduce the risk of irreversible bolus overdose, the FDA withdrew approval for intravenous colchicine.[40,48] Acute overdose usually manifests as gastrointestinal symptoms within 24 hours of ingestion, widespread organ system dysfunction (renal failure, circulatory collapse, marrow failure, muscle weakness, rhabdomyolysis, and respiratory failure) within