Colchicine: Its Mechanism of Action and Efficacy in Crystal-Induced Inflammation

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New light has been shed on the mechanisms of action of colchicine in crystal-associated arthropathies. Colchicine, long used to treat gout, arrests microtubule assembly and inhibits many cellular functions. At micromolar concentrations, it suppresses monosodium urate crystal-induced NACHT-LRR-PYD-containing protein-3 (NALP3) inflammasome-driven caspase-1 activation, IL-1β processing and release, and L-selectin expression on neutrophils. At nanomolar concentrations, colchicine blocks the release of a crystal-derived chemotactic factor from neutrophil lysosomes, blocks neutrophil adhesion to endothelium by modulating the distribution of adhesion molecules on the endothelial cells, and inhibits monosodium urate crystal-induced production of superoxide anions from neutrophils. Cytochrome P450 3A4, the multidrug transporter P-glycoprotein, and the drugs that bind these proteins influence its pharmacokinetics and pharmacodynamics. Trial evidence supports its efficacy in acute gout and in preventing gout flares, but it has narrow therapeutic index, and overdosage is associated with gastrointestinal, hepatic, renal, neuromuscular, and cerebral toxicity; bone marrow damage; and high mortality.

Introduction

Colchicine is an alkaloid extracted from the corm of the meadow saffron or autumn crocus (*Colchicum autumnale*). In one form or another, it has probably been used for the nonspecific treatment of arthritis for nearly 4000 years [1•]. A description of a plant extract similar to colchicine was recorded in the Ebers papyrus in 1550 bc. Hippocrates advocated colchicum or White Hellebore (*Veratrum album*) as a powerful purgative for intractable cases of chronic gouty arthritis, believing that "the best natural relief for this disease is an attack of dysentery." It was nearly 1000 years later that two Byzantine physicians, Alexander of Tralles and Aetius of Amida, described the use of Hermodactyl, extracted from *Colchicum variegate*, a plant similar to *C. autumnale*, as a more specific and selective treatment for acute gouty arthritis. They were the first to appreciate that its therapeutic benefits were distinct from its gastrointestinal (GI) side effects.

However, because of colchicine's powerful purgative effects, its use was virtually discontinued in the Middle Ages in continental Europe after being forbidden by the very influential Abbess Hildegard of Bingen (1098–1179 ad). Colchicine was scarcely used in Britain for nearly 150 years in the 17th and early 18th centuries because of the influence of Thomas Sydenham (known as the "English Hippocrates"), who rejected all purgatives as too toxic.

The value of colchicine for treating gout was rediscovered by Baron Anton de Stoerk in Vienna in 1763, after Nicholas Husson, a French army officer and a quack, marketed a patent medicine containing colchicum. L'Eau d'Husson was introduced in the United States in 1798 by Benjamin Franklin, who used it to treat his own gout. Subsequently, physicians on both sides of the Atlantic enthusiastically adopted colchicine as a gout treatment in the 19th century, after French chemists Pelletier and Caventon identified the pharmacologically active plant constituent in 1820.

In the past 50 years, the use of short courses of fast-acting nonsteroidal anti-inflammatory drugs (NSAIDs) have largely superseded colchicine as the oral drugs of choice for the symptomatic treatment of acute gout [2•] and pseudogout [3] when there are no specific contraindications to their use, because they are considered to have a better benefit-to-risk ratio than that of colchicine. In particular, ongoing concerns exist regarding the GI side effects and the narrow therapeutic margin between efficacy and GI toxicity with the recommended dosage schedules for colchicine. Additional concerns about more remote risks of bone marrow suppression [4], myopathy and neuropathy [5], especially in patients with renal insufficiency [6], and the very high mortality associated with overdosage have led to calls for serious reappraisal of the use of colchicine to treat patients with acute attacks

of gout. However, the efficacy of low-dose prophylactic colchicine, first suggested in 1936 [7], has been substantiated in placebo-controlled, randomized controlled trials (RCTs) in patients commencing urate-lowering drug therapy with allopurinol [8] or probenecid [9].

Although most basic information about the pharmacokinetics, pharmacology, and biologic effects of colchicine was established in the 1960s and 1970s [10], recent advances in understanding the pathophysiology of crystal-induced inflammation have shed new light on the mechanisms of action of colchicine in crystal-associated arthropathies. This review presents a critical appraisal of current evidence relating to the mechanism of action of colchicine in crystal-induced inflammation and its safety and efficacy in treating patients with gout and other crystal-associated arthropathies.

Crystal-Induced Inflammation

Without treatment, acute attacks of gout and pseudogout are characterized by crystal-induced initiation of inflammation, leukocyte recruitment and amplification of the inflammatory response, and spontaneous resolution [11••].

Initiation of inflammation in gout and other crystal-associated arthropathies follows the binding of uncoated, "naked" microcrystals that have highly reactive, negatively charged surfaces [12] to a range of cell surface proteins [13] and plasma membrane receptors on resident tissue macrophages, synovial lining cells, and mast cells. It has been suggested that these include integrins [14] and Toll-like receptors (TLRs), which are responsible for recognition of microbial antigens and initiation of innate immune responses [15••].

Toll-like receptors and innate immune responses

TLRs are transmembrane structures with an ectodomain responsible for ligand recognition, a transmembrane domain, and a cytoplasmic domain with strong structural resemblance to the cytoplasmic portion of the interleukin (IL)-1 receptor (ie, the Toll/IL-1 receptor, or TIR domain). Once stimulated, TLRs associate with a number of intracellular adaptor molecules to trigger a signaling cascade that activates proinflammatory transcription factors such as nuclear factor-κB [16]. The possibility that monosodium urate (MSU) microcrystals, like microbial products, might stimulate innate immune responses was suggested by studies that showed that urate released from injured cells acted as a danger signal to activate the immune system to clear the products from dying cells [17]. In effect, MSU microcrystals could act as adjuvants in stimulating innate immune responses [17]. Using knockout mice and wild-type controls, Liu-Bryan et al. [15••] showed that crystal activation of murine bone marrow-derived macrophages and induction of crystal-induced inflammation by naked MSU microcrystals in a murine synovium-like air pouch model was partly dependent on the presence of TLR2, TLR4, and cytosolic TLR adaptor protein myeloid differentiation factor 88 (MyD88). The inflammatory response triggered by unopsonized crystals included crystal phagocytosis and production of the proinflammatory cytokines IL-1β and tumor necrosis factor (TNF)-α and the neutrophil chemotactic (CXCR2)-binding chemokines keratinocyte-derived cytokine (KC) and growth-related oncogene (GRO) α [15••]. However, Chen et al. [18••] demonstrated that although MyD88 was essential for crystal-induced peritonitis in mice, TLRs and other TLR adaptor proteins were not. MyD88 can function as an adaptor protein in the IL-1 receptor (IL-1R) signaling pathway and in TLR signaling, and these investigators showed that IL-1 production and IL-1R activation were essential for MSU-triggered inflammation in their model systems [18••].

Interleukin-1β processing and the inflammasome

Earlier studies showed that the activation of human mononuclear phagocytes by MSU crystals was associated with upregulation of IL-1 gene expression [19]. However, production of active IL-1β requires production of a precursor protein, pro-IL-1β, maturation of pro-IL-1β, and secretion of the mature IL-1β into the extracellular environment [20]. Pro-IL-1β processing is mediated by caspase-1 after activation in a complex or molecular platform known as an inflammasome [21]. In a landmark paper, Martinon et al. [22••] showed that microcrystals of MSU and calcium pyrophosphate dihydrate (CPPD) can engage the NALP3 inflammasome (cryopyrin) and so stimulate the production of active IL-1β in human monocytes and murine peritoneal macrophages. Macrophages from knockout mice lacking caspase-1, NALP3, or the adaptor protein ASC (apoptosis-associated speck-like protein containing a caspase recruitment domain), which links caspase-1 with NALP3, had defective responses to MSU and CPPD microcrystals [22••]. Murine bone marrow–derived macrophages lacking CD14, a shared TLR2 and TLR4 adaptor molecule, demonstrated attenuated MSU crystal-induced IL-1β release [23•]. Although microcrystal activation of the NALP3 inflammasome seems critical for MSU and CPPD crystal-induced inflammation, the sequence of events by which the extracellular microcrystals are brought in contact with and activate the intracellular inflammasome is still unclear [24•]. MSU crystal activation of the NALP3 inflammasome may require low intracellular potassium concentrations [24•,25], but it is not inhibited by blocking the purinergic P2X7 receptor [22••].

Negatively charged MSU microcrystals can bind to more than 25 serum proteins, including complement components such as C1q, C1r, and C1s [26]. MSU crystals can activate both the classic [27] and alternative [28,29] complement pathways in vitro, with the generation of leukocyte chemotactic fragments such as C3a, C5a [30,31], and iC3b, which can coat crystal surfaces and create ligands for the

neutrophil membrane receptor CR3 (CD11b/CD18) [14]. Although activation of the classic and alternative complement pathways by MSU crystals can occur without crystal opsonization with complement components or immunoglobulins, it is amplified by the presence of both C-reactive protein and IgG [32].

Mononuclear phagocyte activation by MSU crystals is also associated with upregulation of cyclooxygenase (COX)-2 gene expression [33], and phagocytosis of MSU crystals by synovial fibroblasts is followed by release of prostaglandin E2 (PGE2) and other arachidonic acid metabolites [34].

Leukocyte recruitment

Leukocyte recruitment, especially of neutrophils, is a hallmark of crystal-induced inflammation. In patients with acute gouty arthritis, the synovial membrane is intensely infiltrated by neutrophils, mononuclear phagocytes, and lymphocytes [35]. MSU crystal-induced synovitis in dogs can be reversibly inhibited by neutrophil depletion and replacement [36]. Leukocyte influx is preceded by vascular endothelial cell activation with expression of adhesion molecules such as E-selectin, intercellular adhesion molecule-1, and vascular cell adhesion molecule-1, following stimulation by proinflammatory cytokines IL-1β or TNF-α, presumably from monocytes [37] or mast cells [38]. Mononuclear phagocyte activation by MSU crystals is associated with upregulation of gene expression of IL-1 [19], TNF-α [39], IL-6 [40], and IL-8 [41]. Although TNF-α is upstream of IL-1β in the inflammatory cascade in rheumatoid arthritis and some other inflammatory rheumatic diseases, this is not the case in crystal-induced inflammation. TNF-α production is preceded by the release of IL-1β following microcrystal stimulation [22••,37], and it can be inhibited by caspase-1 inhibition without affecting TNF-α production in response to the TLR2 agonist zymosan [22••]. Apparently, monocyte-derived neutrophil chemotactic CXCR2 binding chemokines including KC, GRO-α/CXCL1, and IL-8/CXCL8 are also essential for MSU-induced crystal inflammation development [41,42]. Experiments using C6-deficient rabbits have shown that activation of the terminal membrane attack complex of complement is also crucial for IL-8 generation and neutrophil recruitment in MSU crystal-induced arthritis in the rabbit knee [43].

Neutrophil recruitment is substantially amplified by MSU crystal-induced release of the calgranulin heterodimer S100A8/9 from neutrophils [44]. Neutrophil phagocytosis of microcrystals is also associated with synthesis and release of many other proinflammatory mediators (eg, IL-1β [45], IL-8 [46], PGE2 [47], superoxide anion [48], and other free radicals [49]).

Possible mechanisms contributing to the spontaneous resolution of acute crystal-induced synovitis have been reviewed in detail [11••,50]. They include the coating of crystals with antiopsonic apolipoprotein B [51] and E [52], crystal-induced production of melanocortin peptides [53], inflammation-limiting peroxisome proliferator-activated receptor-γ induction [54], neutrophil apoptosis by macrophages with transforming growth factor-β production [55], and promotion of apoptotic neutrophil uptake by macrophage-derived transglutaminase 2 [56]. Another possible mechanism is a change in the response of macrophages to microcrystals from production of proinflammatory to anti-inflammatory mediators as they differentiate [57].

Mechanisms of Action of Colchicine in Crystal-Induced Inflammation

Colchicine has a range of biologic and pharmacologic effects that could be relevant to its therapeutic efficacy and adverse side effects (Table 1, Fig. 1). It is one of many alkaloids with antimitotic activity that can bind specific sites on subunits of the cytoskeletal protein tubulin to arrest microtubule polymerization [58]. Disruption of normal cytoskeletal assembly leads to inhibition of many essential cellular functions including intracellular vesicle transport and secretion of mediators such as chemokines and cytokines, impairment of cell migration, and inhibition of cell division [59••].

In vitro studies undertaken in the 1960s and 1970s showed that colchicine diminished neutrophil chemotaxis [60] and the mobilization and release of lysosomal enzymes from neutrophils during phagocytosis [61]. Work by Phelps [62] and Spilberg et al. [63], which was recently reviewed by McCarty [64•], established that colchicine in concentrations as low as 0.1 nM inhibited the release of a glycopeptide crystal-derived chemotactic factor (CCF) from neutrophil lysosomes. CCF has a molecular size and amino acid composition close to those of the calgranulin heterodimer S100A8/9, and it has been proposed that they are in fact the same entity [65•]; however, this remains to be proven. McCarty [64•] has suggested evidence that CCF production is blocked by actinomycin D and tunicamycin, that it has localization in the lysosomal fraction, and that it has exquisite sensitivity to colchicine blockade, is somewhat at odds with the known cytosolic location of S100A8/9.

In a landmark paper in the 1990s, colchicine was shown to inhibit polymorph adhesion and mobility following crystal-induced neutrophil activation by selective inhibition of tyrosine phosphorylation and reduction in the generation and release of the chemotactic leukotriene B4 [66]. However, colchicine inhibits neutrophil migration following crystal activation of neutrophils without changes in production of the chemokine IL-8 [67]. Colchicine induces COX-1 and COX-2 gene expression and does not inhibit COX-1 or COX-2 in neutrophils [68].

At relatively high micromolar concentrations, colchicine suppresses MSU crystal-induced NALP3 inflammasome-driven caspase-1 activation, as well as IL-1β processing and release [22••]. The mechanism by which colchicine inhibits its crystal-induced inflammasome activation is currently

Table 1. Mechanisms of action of colchicine in crystal-induced inflammation

Study	Biologic effect	Biochemical basis
Caner [60]	↓ Neutrophil chemotaxis	↓ Tubulin polymerization
Wright and Malawista [61]	Stabilization lysosomes	↓ Tubulin polymerization
Phelps [62], Spilberg et al. [63], McCarty [64•]	↓ Release CCF	↓ Tubulin polymerization
Roberge et al. [66]	↓ Neutrophil activation ↓ Leukotriene B4	↓ Tyrosine phosphorylation
Martinon et al. [22••]	↓ NALP3 inflammasome driven caspase-1, IL-1β processing and release	↓ Tubulin polymerization
Cronstein et al. [70]	↓ Neutrophil L-selectin	↓ Tubulin polymerization
Cronstein et al. [70]	Block IL-1–induced ↑ neutrophil adhesion by change distribution E-selectin on endothelial cells	↓ Tubulin polymerization
Abramson et al. [48], Roberge et al. [66], Minta and Williams [71], Chia et al. [72••]	↓ Neutrophil superoxide anion	↓ Tubulin polymerization

CCF—crystal-derived chemotactic factor; IL—interleukin; NALP3—NACHT-LRR-PYD-containing protein-3.

unknown. Some have speculated that inhibition of microtubule assembly could impair microcrystal delivery to the intracellular inflammasome protein complex [65•,69•] by interfering in some way with the complement membrane attack complex [43] or CD14 [23•] or by preventing the microcrystals from interacting with the leucine-rich repeat domain of the NALP3 inflammasome [69•].

Colchicine interferes with neutrophil adhesion and recruitment to inflamed tissues following MSU crystal stimulation because of suppression of neutrophil L-selectin expression and alterations in the distribution of E-selectin on endothelial cells [70]. At nanomolar concentrations, colchicine blocks the increase in neutrophil adhesion to endothelium in response to IL-1 or TNF by altering distribution of the adhesion molecules on the endothelial cells. At higher concentrations (300 nM), colchicine inhibits L-selectin expression on neutrophils [70]. It has been suggested that these biologic effects might be responsible for the prophylactic effect of colchicine in preventing gout flares at low dosage and its therapeutic effect in relieving inflammation in patients with acute attacks of gout at higher doses [70].

Colchicine has also been shown to have a selective effect in suppressing MSU crystal-induced superoxide anion production in human neutrophils in vitro [66,71]. This effect is likely due to inhibition of microtubule polymerization, as the effect is blocked by paclitaxel [72••], a microtubule-stabilizing agent, but colchicine does not inhibit superoxide anion production by neutrophils in response to N-formyl-met-leu-phe, phorbol esters, or opsonized zymosan [66,71]. Recent studies have demonstrated that MSU crystal-induced superoxide anion production in murine peritoneal macrophages can be inhibited in vivo by colchicine at doses 100 times lower than those required to inhibit neutrophil infiltration [72••], indicating that crystal-induced induction of nicotinamide adenine dinucleotide phosphate (NADPH) oxidase is more sensitive than cell migration to microtubule disruption by colchicine. Some have suggested that the early anti-inflammatory effects of colchicine may be related to inhibition of superoxide anion and other antioxidant effects [48].

Presently, it seems impossible to determine whether the therapeutic efficacy of colchicine in treating gout attacks and preventing flares is mediated primarily by its effects on crystal-induced CCF, leukotriene B4, or superoxide/free radical generation, or on the distribution of adhesion molecules on endothelial cells. Colchicine effects on MSU crystal-induced NALP3 inflammasome-driven caspase-1 activation and IL-1β processing and release seem less likely to be the primary focus for its therapeutic effects in crystal-driven inflammation, because they have not been shown to occur at drug concentrations achieved during therapy.

Pharmacokinetics, Pharmacodynamics, and Metabolism

The pharmacokinetics and pharmacodynamics of colchicine are heavily determined by its interaction and binding to three proteins: tubulin, cytochrome P450 3A4 (CYP3A4), and the multidrug transporter P-glycoprotein (P-gp) [73••].

As previously indicated, most of the pharmacologic effects of the drug result from colchicine binding to tubulin, preventing microtubule assembly, and disrupting cellular functions. The tubulin–colchicine bond has a high dissociation constant, and the half-life of the tubulin–colchicine complex is 20 to 30 hours. Because of the slow rate of dissociation of tubulin-bound drug, colchicine bound in tissues plays a major role in controlling its pharmacokinetics. The volume of distribution of colchicine in the body is considerably larger than the extracellular compartment because of

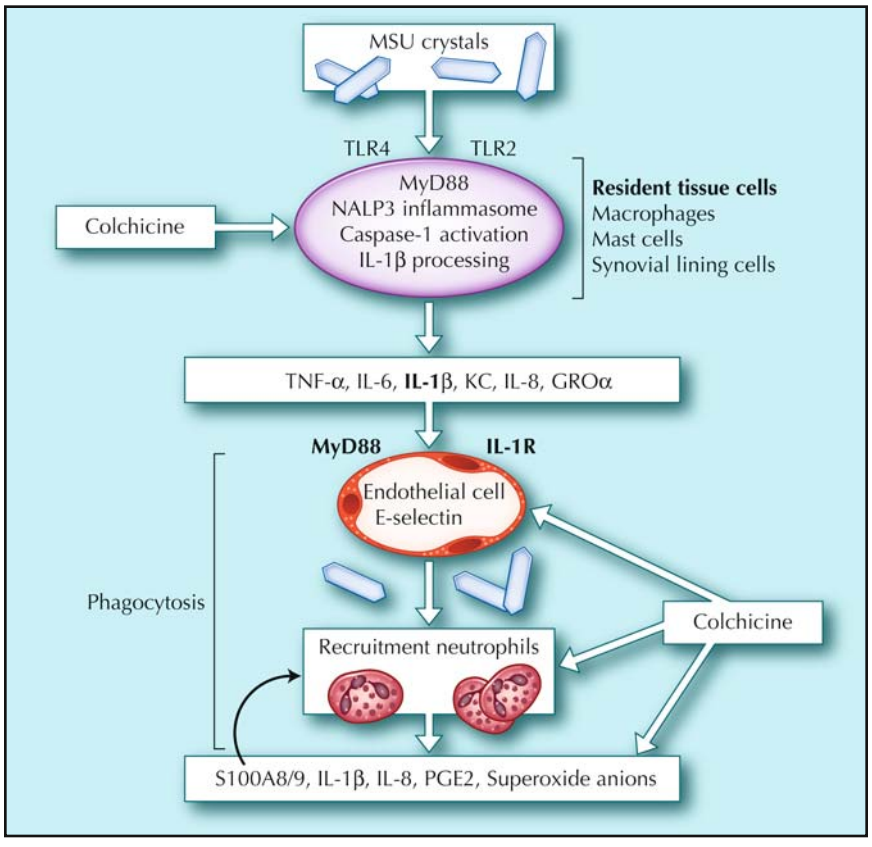

Figure 1. Simplified outline of mechanisms and mediators of crystal-induced inflammation, including main sites of action of colchicine. Monosodium urate (MSU) and calcium pyrophosphate dihydrate (CPPD) microcrystals engage Toll-like receptor (TLR) 2 and TLR4 on resident tissue monocytes/macrophages. In the presence of the cytosolic adaptor protein myeloid differentiation factor (MyD88), the crystals induce the NACHT-LRR-PYD-containing protein-3 (NALP3) inflammasome, caspase-1 activation, interleukin (IL)-1β processing, and the release of IL-1β and other cytokines (eg, tumor necrosis factor [TNF]-α, IL-6) and chemokines (eg, keratinocyte-derived cytokine [KC], IL-8, growth-related oncogene [GRO]-α). The IL-1β and TNF-α released from the resident tissue cells stimulate endothelial cell adhesion molecules (eg, E-selectin) and neutrophil influx. Neutrophil recruitment is amplified by crystal-induced release of S100A8/9, and neutrophil phagocytosis of the microcrystals is followed by release of IL-1β, IL-8, superoxide anions, and prostaglandin E2 (PGE2). At micromolar concentrations, colchicine suppresses MSU crystal-induced, NALP3 inflammasome-driven caspase-1 activation and IL-1β processing and release. At nanomolar concentrations, colchicine blocks the release of a crystal-derived chemotactic factor from neutrophil lysosomes, blocks neutrophil adhesion to endothelium by modulating the distribution of adhesion molecules on the endothelial cells, and inhibits MSU crystal-induced production of superoxide anions from neutrophils.

widespread uptake in tissues. In addition, there is evidence for preferential accumulation of colchicine in red blood cells and neutrophils [74]. Peak plasma concentrations of drug are seen an hour after a single 1-mg oral dose, but peak intracellular concentrations are only achieved after 48 hours [74], which is similar to the time needed to observe biologic effects such as inhibition of chemotaxis [73••]. When colchicine therapy is discontinued, its elimination half-life is about 16 hours, and its biologic effects require 24 to 48 hours to dissipate [73••].

Colchicine is predominantly excreted through the biliary tract after metabolism in the liver, but up to 20% of the drug is cleared by the kidneys, by both glomerular filtration and tubular secretion [75]. Creatinine clearance levels lower than 25 mL/min carry a high risk of colchicine accumulation [76], and the risks of colchicine toxicity are higher in patients with renal insufficiency [6] and chronic liver disease [77]. Colchicine metabolism in the liver has not been investigated in humans, but animal studies and in vitro assays using primary human hepatocyte cultures and hepatic microsomes from in vivo animal experiments have established that colchicine undergoes oxidative demethylation by the main P450 cytochrome CYP3A4 [73••]. Colchicine is often given with other CYP3A4 substrates (Table 2), which can result in significant drug interactions. For example, cimetidine has been associated with a 30% decrease in hepatic clearance of colchicine and prolongation of its plasma elimination half-life [73••].

Colchicine is also one of a wide range of drugs that bind to the adenosine triphosphate–dependent phosphoglycoprotein P-gp, which is widely distributed in cell membranes in the biliary tract, blood–brain barrier, renal tubules, and intestine (Table 2). P-gp influences absorption, distribution, and elimination of its substrates so that co-prescription of inhibitors or modulators can lead to intracellular accumulation of colchicine, with increases in pharmacologic effects or toxicity. For example, cyclosporine has been shown to decrease the renal clearance of colchicine by 50% by inhibiting P-gp facilitated proximal renal tubular secretion of the drug [78], and it has been shown to interfere with biliary excretion of colchicine by a similar mechanism of drug interaction [79]. Co-prescription of verapamil and colchicine led to tetraplegia secondary to inhibition of the P-gp "efflux pump" at the blood–brain barrier by verapamil, resulting in toxic accumulation of colchicine in neural tissues [80].

Clinical Efficacy and Side Effects

Evidence-based recommendations for gout management were published recently by the European League Against Rheumatism Standing Committee for International Studies

Table 2. Examples of drugs with potential to cause colchicine accumulation, increased pharmacologic effects, and toxicity

Cytochrome P450 3A4 inhibitors	P-glycoprotein substrates/modulators
Azole antifungals (ketoconazole and itraconazole)	Amitriptyline
Cimetidine	Cimetidine
Clarithromycin	Cyclosporine
Erythromycin	Digoxin
Fluoxetine	Quinidine
Paroxetine	Erythromycin
Nefazodone	Clarithromycin
Indinavir and other protease inhibitors	Doxorubicin
Tolbutamide	Vinblastine
	Vincristine
	Paclitaxel
	Indinavir and other protease inhibitors
	Loperamide
	Morphine
	Prednisolone
	Dexamethasone
	Progesterone
	Phenytoin
	Simvastatin
	Verapamil

Including Therapeutics [81•] and the British Society for Rheumatology [2•].

Acute gout and pseudogout

Only one small placebo-controlled RCT has demonstrated the efficacy of oral colchicine when administered with a loading dose of 1 mg followed by 0.5 mg every 2 hours until toxic GI side effects of nausea, vomiting, or diarrhea develop [82]. The effect size (ES) was relatively large for pain relief (ES, 0.87; 95% CI, 0.25–1.5) and overall clinical improvement (ES, 1.21; 95% CI, 0.61–1.92); the number needed to treat to obtain greater than 50% pain relief was only 3 (95% CI, 2–11). Pain relief was faster with colchicine than with placebo; most patients responded within 18 hours. However, all 22 patients receiving colchicine developed nausea, vomiting, or diarrhea, compared with 5 of 21 patients in the placebo group (RR, 4.2; 95% CI, 1.95–9.03).

In the hope of retaining efficacy while reducing the frequency of GI side effects, current guidelines recommend treatment of acute gout attacks with smaller and less frequent doses of colchicine (0.5 mg, 2–4 times daily) [2•,81•,83••,84], but this recommendation is based on isolated case reports [85,86] and expert opinion alone. The risks of bone marrow suppression [4], neuromyopathy [5,86], and rhabdomyolysis [87], especially in patients with renal insufficiency [6,86], must also be considered when weighing the risks and benefits. A Cochrane review of colchicine for acute gout recommended the continued cautious use of colchicine as a second-line therapy for acute gout when NSAIDs or corticosteroids are contraindicated or ineffective [88]. Others have questioned the need to retain colchicine in the pharmacopeia for the treatment of acute gout, because of its very narrow therapeutic index [83••]. Overdosage can be associated with acute multisystem failure [89]. Therapeutic doses are usually in the range of 0.015 to 0.03 mg/kg [73••]. Doses in the 0.5 to 0.8 mg/kg range can induce bone marrow failure and carry a 10% mortality, whereas death is the rule after ingestion of more than 0.8 mg/kg [90]. Drug interactions with cyclosporine and erythromycin probably contributed to some cases of fatal colchicine toxicity [91,92], and in one regional center, 8 of 9 cases of colchicine overdosage seen over 15 years were fatal [83••]. A significant number of these cases resulted from accidental overdosage. This finding led to the conclusion that although knowledge of colchicine side effects was widespread, the near certainty of a fatal outcome following a significant overdose was not as widely appreciated [83••]. As a result, the New Zealand Medicines and Medical Devices Safety Authority proposed the following Medsafe Guidelines for using colchicine [93], which are also recommended by others [83••,84]:

- Limit colchicine to second-line therapy.
- Colchicine should not be used unless NSAIDs are contraindicated, have low efficacy, or have unacceptable side effects.
- Colchicine should no longer be taken "until symptoms of GI upset subside."
- Increase dose interval to every 6 hours (from every 2 to 3 hours).
- Reduce maximum dose in the first 24 hours to 2.5 mg.
- Reduce maximum cumulative dose to 6 mg over 4 days (3 mg in elderly patients).
- Reduce dose in hepatic/renal dysfunction, elderly people, and low-weight states.

Because intravenous (IV) administration of colchicine reduces the propensity for GI side effects, some of the most experienced clinical experts recommend the judicious use of IV colchicine to treat patients with acute gout when oral administration is not possible or when there is a great need to avoid GI side effects [64•,94]. However, the risks of renal, hepatic, central nervous system, and bone marrow toxicity are much higher following IV administration. The US Food and Drug Administration received reports of 20

deaths following IV colchicine between 1983 and 2000, 17 of which occurred in patients with gout [95]. This finding led some authorities to suggest elimination of the use of IV colchicine for acute gout treatment [2•,81•,84,96]. The manufacture of IV colchicine in the United States was halted in February 2008 [97], following reports of deaths attributable to compounding pharmacy errors [98]. Any future IV colchicine preparation will require approval from the US Food and Drug Administration. If it is to be used intravenously, McCarty [64•] recommends a small dose (1 mg), whereas earlier published guidelines for the safe administration of IV colchicine are as follows [94,99]:

- Initial dose of 2 mg through established IV catheter to minimize toxic extravasation risk.
- If necessary, two additional doses of 1 mg at 6-hour intervals.
- Total dose should never exceed 4 mg.
- Doses should be reduced by at least 50% in elderly patients and in patients with hepatic or renal disease.

General agreement exists that IV colchicine should never be given to patients who have already been treated orally with colchicine.

Small oral colchicine doses (0.5 mg once or twice a day) are sometimes given empirically in combination with other anti-inflammatory medications (ie, NSAIDs, intra-articular corticosteroids, or systemic corticosteroids) to control inflammation in patients with difficult, prolonged, subacute gouty arthritis when there are no contraindications. However, no controlled trials have been undertaken to demonstrate the efficacy or safety of such combination therapy. No RCTs support the use of oral colchicine to treat acute pseudogout or calcific periarthritis, although the drug is used for treating these conditions [64•].

Prophylactic use of colchicine

The efficacy of prophylactic oral colchicine, 0.5 mg once a day for 6 months [9] or 0.6 mg twice a day for 3 months [8], was demonstrated in two placebo-controlled RCTs in patients commencing urate-lowering drug therapy with probenecid (ES, 0.74; 95% CI, 0.08–1.40) [9] or allopurinol (number needed to treat, 2; 95% CI, 1–6) [8]. Diarrhea was a problem in 38% of patients receiving colchicine, 0.5 mg twice a day, with a relative risk compared to placebo of 8.38 (95% CI, 1.14–61.38) [8], but GI side effects were not increased in patients only receiving 0.5 mg colchicine [9].

In a study of colchicine prophylaxis in 10 patients who had had recurrent attacks of pseudogout, patients were followed for a year before and after receiving colchicine, 0.6 mg twice a day, and investigators found a reduction in acute attacks from 3.2 per year to 1 per year [100].

Colchicine is used to treat patients who have refractory CPPD-associated arthropathies [101], but good controlled trial data to support its efficacy for this purpose are lacking. Clinical experience suggests that basic calcium phosphate–associated arthropathies are best managed with NSAIDs and/or intra-articular or periarticular injections of corticosteroids.

Conclusions

Despite a paucity of appropriately designed RCTs, sufficient clinical evidence suggests that oral colchicine, 0.5 mg two or three times a day, can be used safely and effectively as a second-line agent for treating acute attacks of gout when NSAIDs and corticosteroids are contraindicated or ineffective. However, higher or more frequent doses are associated with an unacceptably high incidence of GI side effects. IV colchicine, which is associated with fewer GI side effects, should not be used because of significantly greater risks of renal, hepatic, central nervous system, and bone marrow toxicity. Colchicine has an exceptionally narrow therapeutic index, and overdosage is associated with multiorgan failure and a very high mortality. Nevertheless, small prophylactic doses of colchicine (0.5 mg once or twice a day) are the prophylactic treatment of choice for preventing flares of acute gout following the commencement of uric acid–lowering drug therapy. Much less evidence exists for the efficacy of colchicine for treating or preventing CPPD-associated pseudogout or for treating refractory CPPD-associated arthropathies or basic calcium phosphate–associated periarthritis; RCTs of colchicine for treating these conditions need to be undertaken.

Disclosure

The author has reported no potential conflicts of interest relevant to this article.

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have been highlighted as:
- • Of importance
- •• Of major importance

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