Update on Colchicine and Its Mechanism of Action

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Colchicine is a unique anti-inflammatory drug with respect to its limited clinical usefulness and its mode of action. Colchicine is mainly indicated for the treatment and prophylaxis of gout and familial Mediterranean fever. Its mode of action includes modulation of chemokine and prostanoid production and inhibition of neutrophil and endothelial cell adhesion molecules by which it interferes with the initiation and amplification of the joint inflammation. This paper discusses its adverse effects and indications.

Introduction

Colchicine, originally extracted from *Colchicum autunale*, is an anti-inflammatory drug that has been in continuous use for more than 3000 years [1]. Although colchicum was first mentioned as a remedy (named hermadactyl or finger of Hermes) for acute gouty arthritis in the "Therapeutica" of Alexander of Tralles (5500 AD), a drug that was probably identical to colchicine was described in the Ebers papyrus (1500 AD). Colchicine was later reintroduced as a drug for gout in 1764 by Baron Anton von Storch, physician to Empress Maria Theresa. In 1820, Pelletier and Caventou [2] were the first to extract colchicine as the active alkaloid of colchicum.

This review discusses the clinical and pharmacologic aspects of colchicine in the management of gout.

Pharmacokinetics

Among the unique features of colchicine is its low therapeutic index. Effective steady-state plasma concentrations after acute treatment range from 0.5 to 3 ng/mL, with toxic effects occurring at a level of approximately 3 ng/mL. Colchicine is a neutral and highly lipid-soluble compound at physiologic pH (measure of acid strength [pKa] = 12.8; molecular weight [MW] = 398), which enables its rapid passage into body tissues. After an intravenous dose of 2 mg colchicine, the plasma half-life is 19.3 ± 7.5 minutes [3,4]. After oral administration, colchicine is absorbed in the jejunum and ileum with a single zero-order rate process, with 44% bioavailability [5]. It binds with low affinity to albumin (32% bound) [6] and possesses a large steady-state volume of distribution [7]. Serum colchicine concentration declines in a bi-exponential mode, reflecting its rapid clearance from the plasma and its rapid redistribution to leukocytes [8] and red blood cells [6]. Most of the administered dose of the drug is metabolized. Only 10% to 25% of an oral dose is recovered unchanged in the urine. Its peak plasma concentration after oral administration is achieved after approximately 2 hours. Colchicine has a plasma half-life of approximately 4 hours, although it can be detected in leukocytes for up to 10 days after administration. Colchicine is excreted mainly in the urine; thus its plasma half-life is prolonged in patients with renal failure, especially in those with combined renal and liver diseases [9]. Patients with renal or liver diseases who take colchicine should be monitored carefully for possible toxic effects of the drug.

Mechanism of Action

Colchicine exerts its therapeutic effect by interfering with several steps involved in the inflammatory process that takes place during gouty arthritis. Colchicine does not have any effect on the formation of monosodium urate crystals or their dissolution. Similarly, it does not affect serum or urine urate concentration [6,10].

Colchicine was long known to inhibit cell division and proliferation. Early studies demonstrated that colchicine disrupts the mitotic spindle. Dissolution of microtubules subsequently was shown to be responsible for the effect of colchicine on the mitotic spindle and cellular proliferation [11,12]. Although colchicine was previously known to affect a variety of neutrophil functions, Malawista and Bensch [11] first demonstrated that, similar to other cells, neutrophils possess microtubules. Bessis and Breton-Gorius [13] discovered that colchicine disrupts microtubules in a dose-dependent fashion. Microtubules are labile structures that lengthen or shrink by elongation at one end and dissolution at the other. Colchicine does not enhance the rate of microtubule dissolution but inhibits the process of microtubule self-assembly in a substoichiometric fashion by binding β-tubulin with the formation of tubulin-colchicine complexes [12,14,15]. Most of the

pharmacologic effects of colchicine on the cells involved in gouty inflammation appear to be related to the capacity of colchicine to disrupt microtubules. That colchicine is a better prophylactic than therapeutic agent and that it is most effective when used early in treatment suggest that there is a critical, early, microtubule-dependent and colchicine-sensitive pro-inflammatory event in acute gouty arthritis and familial Mediterranean fever (FMF). Later on, this effect is less important for the propagation and amplification of the inflammatory response [16].

Neutrophils constitute most of the cells present in the synovial fluid in acute gouty arthritis. The disappearance of neutrophils is associated with the end of the acute attack. Colchicine modulates various actions of activated neutrophils that are pivotal in the generation of crystal-induced inflammation. Recent studies have introduced new information on the pathogenesis of crystal-induced arthritis [17••]. During inflammation, many soluble mediators are generated that may recruit and stimulate neutrophils. Many of these mediators are thought to play a major role in the pathogenesis of acute gouty arthritis [18,19]. The monokine tumor necrosis factor-alpha (TNFα) is produced by monocytes and synovial cells on contact with monosodium urate crystals [18]. Colchicine inhibits the synthesis of TNFα by macrophages and down-regulates the surface expression of TNFα-receptor on macrophages and endothelial cells [20,21]. Diminished TNFα secretion may interfere with the priming effect of TNFα on neutrophils before their activation by monosodium urate crystals [17••]. Colchicine may also diminish the recruitment of neutrophils to the affected joint by inhibiting the urate crystal-induced [22] and ionophore-induced formation of leukotriene B_4 (LTB_4) [23] and suppressing the locomotion of neutrophils in in vivo studies [24,25]. Monosodium urate crystals induce monocyte-derived interleukin-8 production and release through activator protein 1 (AP-1) and nuclear factor κB (NFκB)-dependent transcriptional activation pathways, which account for neutrophil ingress in acute gouty arthritis [26••]. Colchicine mediates the effects described earlier at concentrations that are generally not achieved in patients. That colchicine is rapidly partitioned to the leukocyte compartment in patients may explain how these lower, pharmacologically relevant concentrations of colchicine are magnified in the leukocytes of patients, thereby regulating inflammation. Even in vitro, colchicine effects are a function of concentration and time of incubation. On monosodium urate crystal-induced activation, there is a marked increase in cyclooxygenase (COX)-2 de novo synthesis, which correlates with the synthesis of prostaglandin E_2 and thromboxane A_2 by mononuclear phagocytes [28•]. Colchicine blocks this COX-2 and prostanoid synthesis, by which it probably reduces the extent of joint swelling and pain in gout [28•].

Neutrophils are recruited into the inflamed joint from the circulation. It was recently noted that the endothelium plays an active role in neutrophil recruitment. When studied in an in vivo model of acute inflammation, colchicine reduces the adhesion of neutrophils to the vascular endothelium [29,30]. The interaction of neutrophils and other circulating leukocytes with the vascular endothelium is mediated by several specific cell adhesion molecules on the neutrophil and the endothelial cell. The molecules responsible for leukocyte-endothelial interaction include members of the integrin family (β_2 integrins on the neutrophil), immunoglobulin superfamily (intercellular adhesion molecules 1 and 2 on endothelial cells), and selectin family (L-selectin on neutrophils, P- and E-selectin on endothelial cells) [31]. When studied in vitro, colchicine abrogates the E-selectin–mediated adhesiveness of the cytokine-stimulated vascular endothelium for neutrophils [32]. The effect of colchicine on E-selectin–mediated endothelial adhesiveness is microtubule-dependent and occurs at concentrations of colchicine that are more than 1000-fold less than those required to affect neutrophil function. Relatively low doses of colchicines (usually 1 mg every day) are administered to patients to prevent acute gouty attacks. The capacity of very low doses of colchicine to modulate endothelial-mediated recruitment of neutrophils to gouty joints may account for the prophylactic effects of the drug. At higher concentrations (10-fold lower than those required to modulate neutrophil lysomal enzyme release or LTB_4 secretion in vitro), colchicine reduces the surface expression or L-selectin on leukocytes and may interfere with the directed movement ("rolling") of neutrophils along the vascular endothelium toward the inflamed joint. Administration of therapeutic doses (but not prophylactic doses) of colchicine markedly reduce L-selectin expression on the neutrophils of normal volunteers, suggesting that this phenomenon also plays a role in diminishing the inflammation of acute gouty attacks [32].

At higher concentrations achievable therapeutically, colchicine exerts various other anti-inflammatory effects including suppression of phospholipase A_2 activation [33], lysosomal enzyme release, and phagocytosis [34,35]. In addition, colchicine interacts with the signal transduction mechanisms within leukocytes that operate during crystal-induced inflammation. Neutrophil activation induced by chemotactic factors and inflammatory microcrystals is accompanied by protein tyrosine phosphorylation and by the activation of the NADPH (nicotinamide adenine dinucleotide phosphate, reduced form) oxidase. Colchicine dose-dependently inhibits crystal-induced neutrophil tyrosine phosphorylation and superoxide anion production through microtubule-related mechanisms [36,37]. These studies further emphasize that colchicine inhibits specific intracellular inflammatory pathways involved in crystal-induced neutrophil activation.

Other effects of colchicine that are not completely related to microtubule disruption include inhibition of arachidonate release and 5-lipoxygenase action in alveolar macrophages [38], suppression of delayed hypersensitivity reactions [39], histamine, insulin, and parathyroid

Table 1. Guidelines and restrictions for intravenous colchicine administration [46]

Nonsteroidal anti-inflammatory drugs, steroids, or corticotropins are preferred whenever oral colchicine is contraindicated or intolerable for the therapy of acute gouty arthritis.
Do not administer intravenous and oral colchicine therapy concomitantly. If the patient has not responded to colchicine or is already being administered maintenance colchicine, an alternative drug should replace further colchicine.
Reduce the dose by at least 50% in patients with renal or hepatic disease and in elderly patients. Do not use the drug at creatinine clearance < 10 mL/minute. Colchicine is not removable by dialysis or exchange transfusion.
Do not administer to patients with combined liver and kidney disease.
Administer the intravenous dose cautiously and slowly to minimize the risk of extravasation.
A single intravenous dose should not be greater than 2 to 3 mg, and no more than a cumulative total dose of 4 mg.
Based on these precaution guidelines, an initial intravenous dose of 2 mg should be administered through an established intravenous line, to be followed by two additional doses of 1 mg each at 6-hour intervals. The total dose should never exceed 4 mg [47].

hormone release [40–42], and induction of apoptosis in mice cerebellar cells [43].

Clinical Use

Colchicine is indicated for the treatment of acute attacks of gouty arthritis, for prophylaxis during the intercritical phase and in the late chronic tophaceous phase of the disease, for prophylaxis of FMF attacks, and prevention of the development of amyloidosis in this disease.

In patients with acute gouty attack, colchicine can be administered orally or intravenously, although nonsteroidal anti-inflammatory drugs are considered to be the drug of choice [44]. Most patients administered colchicine respond within 18 hours; joint inflammation subsides in 75% to 80% of the patients within 48 hours [45]. Only one double-blind placebo-controlled trial has been performed on the effectiveness of oral colchicine in the treatment of acute gout. Clinical improvement was reported within 48 hours in two-thirds of the patients treated with colchicine, most often preceded by gastrointestinal side effects [45]. The drug is usually administered orally in an initial dose of 1 mg, followed by 0.5 mg every 2 hours until gastrointestinal side effects occur, or a total dose of 6 mg has been administered. This procedure is usually safe, unless the patient has renal or liver disease or is elderly [44]. Although the drug is available for intravenous administration, the risk of serious, and even fatal, toxic effects have encouraged the removal of the intravenous preparation from the pharmacopoeia [45]. Fatal toxic effects caused by intravenous colchicine administration, most of which were suicide deaths, or after combined oral and intravenous administration have limited the indications for the use of intravenous colchicine in the management of acute gouty arthritis. Should intravenous colchicine be administered, physicians should follow the guidelines and restrictions provided in Table 1 [46,47].

Colchicine can be used to prevent acute attacks, as has been shown in a placebo-controlled study [48]. An oral dose of 0.5 to 1 mg daily diminished the frequency of acute attacks, regardless of whether the serum urate level was normal. It is recommended to administer low-dose colchicine before the initiation of drugs to correct the hyperuricemia (such as allopurinol). This should be continued for 1 year after the serum urate concentration has returned to a normal level [44].

Adverse Reactions and Toxicity

When colchicine is administered orally to patients with normal renal and hepatic function, the drug is usually safe, although gastrointestinal discomfort occurs in most patients for 24 hours [44,45]. Diarrhea, vomiting, and abdominal cramps are the most frequent side effects of colchicine and are often the first signs of toxicity, indicating that the drug should be stopped. Prolonged high dosage can lead to malabsorption. Bone marrow suppression is rare. Long-term colchicine administration can result in ovarian and testicular dysfunction [49•]. Neuromuscular toxicity was reported in patients with renal failure, usually resolving after the drug was stopped [49•]. Poisoning from colchicine overdose, usually with suicidal intent, when the dose of 0.8 mg/kg is exceeded, is uniformly fatal and characterized by multi-organ failure, starting with gastrointestinal symptoms, dehydration, and leukocytosis, followed by bone marrow suppression, renal failure, adult respiratory distress syndrome, arrhythmias and heart failure, fever, coagulopathy, acid-based disturbances, and neuromuscular involvement [49•]. Recently, colchicine-specific Fab (fragment, antigen-binding [of immunoglobulin]) was reported as effective therapy for colchicine intoxication [50].

Conclusions

Colchicine is the oldest anti-inflammatory agent used in clinical practice in the management of gout and FMF. The unique mechanism of action of colchicine has broadened our understanding of cell biology and of the pathogenesis and control of acute inflammation.

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