Focus

Colchicine in dermatology

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INTRODUCTION

Colchicine, a toxic natural product, which is the active principle of the plant, *Colchicum autumnale* (autumn crocus or meadow saffron), and other plants of Colchiaceae family. It is a nitrogen-containing substance often described erroneously as an alkaloid, although its biosynthetic precursor, demecolcine, is an alkaloid.[1] It has been known since antiquity for its medicinal uses. It is still in use today for the treatment of gout and familial Mediterranean fever.[2] Under suitable qualified medical supervision, isolates from the seeds and tubers of these plants have been used in the treatment of certain skin disorders. Colchicine, was first isolated in 1820 by the two French chemists P.S. Pelletier and J. Caventon.[3] We briefly review here the pharmacological and the therapeutic profiles of colchicine in dermatology.

MECHANISM OF ACTION

Anti-mitotic

Its capacity to interrupt mitosis is due to its linkage to dimers of tubulin, a dimeric protein in microtubules.[4]The microtubular toxicity will cause cessation of mitosis in metaphase and interference in cellular mobility.

Anti-inflammatory

Colchicine reduces mobility, adhesiveness, and chemotaxis of polymorphonuclear cells. It interferes with intercellular adhesion molecules, selectins, thus inhibiting T-lymphocyte activation and its adhesion to endothelial cells.[5,6]

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It impairs cellular secretion of procollagen and increases collagenase production that promotes a larger collagenolytic action.[7]

Immunosuppressive action

It inhibits cell-mediated immune responses,[8] by inhibiting immunoglobulin secretion, IL-1 production, histamine release and HLA-DR expression.

Other pharmacological effects

Decrease of the corporal temperature, depression of the respiratory center, increased response to sympathomimetic agents, contraction of blood vessels, hypertension by central vasomotor stimulation, and alteration of the neuromuscular function. [Figure 1]

PHARMACOLOGY AND PHARMACOKINETICS

It occurs as pale to greenish yellow crystals or powder. When exposed to ultra-violet radiation, it oxidizes into a dark color[9] and is transformed into different photoisomers.[10] Hence, it must be shielded from exposure to sunlight. It is rapidly absorbed when taken orally; peak plasma levels are reached between 30 and 120 min after ingestion. Fifty percent of the drug circulates and links to plasma proteins. The drug is metabolized in the liver, and the majority is eliminated through bile in the feces. It is also distributed in spleen

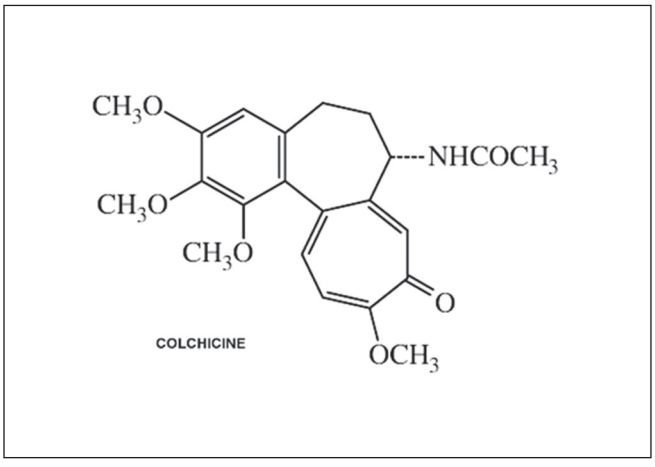

Figure 1: Structure of colchicine

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and kidney. Overall, 10-20% of the dose is eliminated unchanged in the urine.

DOSAGES AND ADMINISTRATION

Oral

Acute gout

Initial dose is 1 mg, reduced to 0.5 mg every 2-3 h, until pain relief is achieved or gastrointestinal toxicity occurs. Course may be repeated after at least 3 drug-free days. Maximum dose: 6 mg/course. Should be stored in an airtight container and protected from light. Initiation of allopurinol treatment must be preceded by daily oral colchicine for at least 2 weeks. This is done as sudden discontinuation of allopurinol results in rapid re-elevation of serum uric acid to pre-treatment levels. Continuation of colchicine for several weeks or months after initiation of allopurinol is recommended by most experts. In patients with tophi, it is advised to continue colchicine prophylaxis until all tophi have dissolved, which often takes years.

Prophylaxis of recurrent gouty arthritis

Adult: 0.5-0.6 mg once daily. Dosage range: 0.6 mg every other day to 0.6 mg tid.

Intravenous preparation (iv)

It is given in 0.9% saline (but not in 5% dextrose as it may precipitate) in a dose of 0.5 mg/mL (2 mL). Single intravenous dosages should not exceed 2-3 mg, and cumulative total dosages for an attack should not be more than 4-5 mg. The administration of iv colchicine is contraindicated in patients with renal failure, extrahepatic biliary obstruction, or patients with combined renal and hepatic insufficiency. Although not approved by the Food and Drug Administration (FDA), intravenous (iv) colchicine has been an accepted treatment for acute gout symptoms. Several additional iv uses include treatment of familial Mediterranean fever, pericarditis, primary biliary cirrhosis, amyloidosis, and Behçet's syndrome.[11-13]

It should not be given intramuscularly or subcutaneously, as it causes severe local irritation.

USES IN DERMATOLOGY

Until now, there was no formal indication approved by the FDA for colchicine use in dermatology; however, several uncontrolled studies have showed exciting results [Table 1], mainly in neutrophilic dermatoses.

Table 1: Labelled indication

Treatment of acute gout and familial Mediterranean fever
Off-label indications of colchicine in dermatology
Gout: cutaneous manifestations[14]
Papulosquamous dermatoses
Psoriasis[15-20]
Recurrent aphthous stomatitis[21]
Behcet's syndrome[22-24]
Sweet's syndrome[25]
Bullous Diseases
Dermatitis herpetiformis[26]
Linear IgA disease[27]
Epidermolysis bullosa acquisita[28]
Chronic Bullous Dermatosis of Childhood[29]
Vasculitis: Leucocytoclastic vasculitis (LCV) and Urticarial vasculitis[30]
Scleroderma[31]
Amyloidosis[32-34]
Miscellaneous[35-47]

Gout

Colchicine controls acute attacks by suppressing 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.[14] It will not prevent the formation of cutaneous tophi and may, actually increase the development of tophi, by preventing the inflammatory response. Hence, hyperuricemia must be controlled at the same time.

Papulosquamous Dermatoses

Psoriasis was one of the first cutaneous diseases to be treated with colchicine. Wahba and Cohen used oral colchicine in 22 psoriasis patients and found greater than 50% improvement in 11 patients. The results were better in those whose lesions were small papules and plaques.[15] Kaidbey *et al.* observed usefulness of topical colchicine in patients with recalcitrant plaque psoriasis.[16] This drug is effectively used in psoriatic arthritis.[17] However, it was not found beneficial in a larger study. Colchicine was found to be effective in generalized pustular psoriasis and palmoplantar pustulosis.[18-20] It is likely that colchicine has a limited therapeutic value in psoriasis.

Recurrent aphthous stomatitis

Colchicine in the dose of 0.6 mg twice or thrice daily was found to decrease morbidity.[21]

Behcet's syndrome

Colchicine was found to be effective in Behcet's syndrome in the treatment of ocular, articular, oral, and genital lesions.[22-24] It was postulated that by blocking

phagocytosis, colchicine may increase superoxide scavenging activity of neutrophils which is impaired in this syndrome.

Sweet's syndrome

Improvement with a daily dose of 1.5 mg colchicine was found in Sweet's syndrome.[25]

Bullous diseases

Several bullous diseases can be treated with colchicine.

Dermatitis herpetiformis

Silvers *et al.* used colchicine at the dose of 1.2-1.8 mg/day to treat patients with dermatitis herpetiformis.[26] They found it useful as alternate therapy in those who could not take sulfonamides.

Linear IgA disease

Aram found colchicine to be very useful in patients who failed to respond to dapsone.[27] The good response to colchicine in this disease may be based on the fact that there are many neutrophils.

Epidermolysis bullosa acquisita (EBA)

Megahed and Scharrffetter-Kochanek described successful treatment of EBA with colchicine.[28]

Chronic bullous dermatosis of childhood

Colchicine was found to be very useful in chronic bullous dermatosis of childhood (CBDC) with G6PD deficiency.[29]

In all the immunobullous dermatoses listed where colchicine is used, dapsone is the better choice and colchicine is an alternative where the patient cannot take dapsone due to G6PD deficiency or some other reason or dapsone is not effective in a particular patient.

Vasculitis

Leucocytoclastic vasculitis (LCV) and Urticarial vasculitis

Several case reports have described the beneficial effects of colchicine in this condition with involvement of the skin, with or without joint manifestations, and also in urticarial vasculitis.[30] Colchicine was effective in urticarial vasculitis associated with hypocomplementemia. It reduces neutrophilic chemotaxis and motility in both these conditions.

Scleroderma

Some authors have described beneficial effects in localized and systemic scleroderma,[31] whereas others have not. Colchicine's action on production, regulation of collagen, adhesion molecules, and matrix digester enzymes justifies its use in this disease.

Amyloidosis

Cutaneous lesions develop in upto 40% of patients with systemic amyloidosis, both primary and secondary. This drug prevents amyloid deposition and slows disease progression in amyloidosis associated with familial Mediterranean fever.[32] Amyloid originates from degenerated epidermal cells in susceptible subjects. Colchicine probably blocks the release of lysosomal enzymes within these cells thereby preventing conversion of the cells tonofilaments into amyloid.[33] Oral colchicine is useful in the management of primary cutaneous amyloidosis.[34]

Miscellaneous

Colchicine was found to be effective in erythema nodosum leprosum,[35,36] pyoderma gangrenosum,[37] severe cystic acne,[38] calcinosis cutis,[39] keloids, sarcoid, condyloma acuminata,[40] fibromatosis,[41] relapsing polychondritis,[42] primary anetoderma,[43] subcorneal pustular dermatosis,[44] erythema nodosum,[45] scleredema,[46] and actinic keratosis.[47]

ADVERSE EFFECTS

Colchicine is usually well tolerated. Gastrointestinal (GI) adverse effects are the most frequent and include diarrhea, nausea, vomiting, and abdominal pain. The GI side effects are due to increase in gut motility by neural mechanisms as well as by inhibition of mitosis in its rapid turnover mucosa. Symptoms decrease on reducing the dose. The iv administration of the drug avoids the occurrence of these gastrointestinal side effects. Long-term therapy may induce steatorrhea, malabsorption with reduced absorption of vitamin B_{12}, fat, sodium, potassium, nitrogen, xylose, and other actively transported sugars. It can cause decreased serum cholesterol and carotene concentrations.

Bone marrow suppression –agranulocytosis, thrombocytopenia, and aplastic anemia occurs after prolonged treatment. Colchicine-induced leukopenia occurs with accidental or intentional overdose and prompt administration of G-CSF must be considered in such cases.

Myopathy and neuropathy occur particularly in

patients with renal impairment. Colchicine induces autophagic vacuolar changes in muscle. Myopathy presents as proximal muscle weakness, with rise in creatinine phosphokinase, abnormal proximal muscle fibrillations, and axonal neuropathy. Myopathy recovers on withdrawal of colchicine. Neuropathy resolution is more prolonged. Azoospermia is a reported side effect.[48]

Dermatological adverse effects include urticaria,[49] toxic epidermal necrolysis,[50] and precipitation of porphyria cutanea tarda. Alopecia occurs 2-3 weeks after the onset of therapy and involves face, axilla, and pubic area.[51]

COLCHICINE OVERDOSE

Colchicine has been known for centuries as a poison. Advice on the dangers of colchicine varies from one source to the next. Until recently, there was no maximum dose of colchicine stated in the approved dosage guidelines. There have been published cases of death occurring after colchicine doses as little as 6 or 7 mg.[52] Overdosage can lead to cholera-like syndrome with dehydration, hypokalemia, hyponatremia, metabolic acidosis, renal failure, and ultimately shock. Respiratory distress syndrome, disseminated intravascular coagulation, and bone marrow suppression occur. Patients may develop convulsions, delirium, muscle weakness, neuropathy, and muscle paralysis. After prolonged therapy, leukopenia, aplastic anemia, myopathy and alopecia can occur. Colchicine intoxication is characterized by multi-organ involvement and by the poor prognosis associated with administration of large amounts of the drug. Therapy is basically supportive and symptomatic because of the rapid distribution and binding of colchicine to the affected tissues. Use of anticolchicine antibodies is a novel approach still in an experimental stage.[53]

DRUG INTERACTIONS

The coadministration of colchicine with known inhibitors or substrates of CYP3A4 may inhibit its metabolism resulting in toxicity such as by macrolide antibiotics. It may increase the serum concentration of cyclosporine, and verapamil, and vice versa. It may cause malabsorption of vitamin B_{12} leading to megaloblastic anemia. Coadministration of simvastatin with colchicine may induce acute myopathy.[54]

MONITORING GUIDELINES

It is suggested that complete blood counts, platelet count, serum multiphasic analysis (i.e. tests of renal and hepatic function), and urinalysis be performed at least every 3 months. Monthly laboratory monitoring for the first few months of therapy is a reasonable protocol. Colchicine should not be used during pregnancy (risk of teratogenicity)[55]

CONCLUSION

Colchicine has many useful actions in dermatological disorders and is well tolerated. Although colchicine is not a first-line medication for any of the conditions mentioned, we are more likely to use it early in patients with leukocytoclastic vasculitis, Sweet's syndrome, and aphthous ulcers. This medication is inexpensive and safe in moderate doses than most immunosuppressive agents.

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