GOUTEX

Tablets

Composition
Each tablet contains Colchicine 0.5mg

Action
Colchicine's effectiveness as a treatment for gout has been postulated to be due to its ability to block neutrophil-mediated inflammatory responses induced by monosodium urate crystals in synovial fluid. Colchicine disrupts the polymerization of β-tubulin into microtubules, thereby preventing the activation, degranulation, and migration of neutrophils to sites of inflammation. Colchicine also interferes with the inflammasome complex found in neutrophils and monocytes that mediates interleukin-1β (IL-1β) activation.

Pharmacokinetics

Absorption

Absolute bioavailability is reported to be approximately 45%.

Administration with food has no effect on the rate or extent of colchicine absorption. Colchicine is not effectively removed by hemodialysis.

Distribution

Colchicine has a mean apparent volume of distribution in healthy young volunteers of approximately 5 to 8 L/kg. Colchicine binding to serum protein is about 39%, primarily to albumin. Colchicine crosses the placenta and distributes into breast milk .

Metabolism

A published in vitro human liver microsome study showed that about 16% of colchicine is metabolized to 2-O-demethylcolchicine and 3-O-demethylcolchicine (2- and 3-DMC, respectively) by CYP3A4. Glucuronidation is also believed to be a metabolic pathway for colchicine.

Excretion

In a published study in healthy volunteers, 40 to 65% of the total absorbed dose of colchicine (1 mg administered orally) was recovered unchanged in urine. Enterohepatic recirculation and biliary excretion are also believed to play a role in colchicine elimination. Colchicine is a substrate of P-gp and P-gp efflux is postulated to play an important role in colchicine disposition. Elimination half-life in humans was found to be 31 h (range 21.7 to 49.9 h).

Special Populations

There is no difference between men and women in the pharmacokinetic disposition of colchicine.

Pediatric Patients

Pharmacokinetics of colchicine was not evaluated in pediatric patients.

Elderly

Pharmacokinetics of colchicine have not been determined in elderly patients. A published report described the pharmacokinetics of 1 mg oral colchicine tablet in four elderly women compared to six young healthy males. The mean age of the four elderly women was 83 years (range 75 to 93), mean weight was 47 kg (38 to 61 kg) and mean creatinine clearance was 46 mL/min (range 25 to 75 mL/min). Mean peak plasma levels and AUC of colchicine were two times higher in elderly subjects compared to young healthy males. It is possible that the higher exposure in the elderly subjects was due to decreased renal function.

Renal Impairment

Pharmacokinetics of colchicine in patients with mild and moderate renal impairment is not known. A published report described the disposition of colchicine (1 mg) in young adult men and women patients who had end-stage renal disease requiring dialysis compared to patients with normal renal function. Patients with end-stage renal disease had 75% lower colchicine clearance (0.17 vs. 0.73

L/hr/kg) and prolonged plasma elimination half-life (18.8 hrs vs. 4.4 hrs) as compared to subjects with normal renal function.

Hepatic Impairment
Published reports on the pharmacokinetics of intravenous colchicine in patients with severe chronic liver disease, as well as those with alcoholic or primary biliary cirrhosis, and normal renal function suggest wide inter-patient variability. In some subjects with mild to moderate cirrhosis, the clearance of colchicine is significantly reduced and plasma half-life prolonged compared to healthy subjects. In subjects with primary biliary cirrhosis, no consistent trends were noted. No pharmacokinetic data are available for patients with severe hepatic impairment (Child-Pugh C).

Pharmacodynamics
The exact mechanism of action of Colchicine in gout is not known. It is involved in leukocyte migration inhibition; reduction of lactic acid production by leukocytes which results in a decreased deposition of uric acid; interference with kinin formation and reduction of phagocytosis with inflammatory response abatement.

Colchicine apparently exerts its effect by reducing the inflammatory response to the deposited crystals and also by diminishing phagocytosis.

Colchicine diminishes lactic acid production by leukocytes directly and by diminishing phagocytosis and thereby interrupts the cycle of urate crystal deposition and inflammatory response that sustains the acute attack.

The oxidation of glucose in phagocytizing as well as in nonphagocytizing leukocytes in vitro is suppressed by Colchicine.

Colchicine is not an analgesic, although it relieves pain in acute attacks. It is not a uricosuric agent and will not prevent the progression of gout to chronic gouty arthritis. It has a prophylactic, suppressive effect which helps reduce the incidence of acute attacks and relieve the patients occasional residual pain and mild discomfort.

Colchicine can produce a temporary leukopenia which is followed by leukocytosis.

Indications
• Treatment of acute gout
• Prophylaxis of gout attack during initiation of therapy with allopurinol and uricosuric drugs

Contraindications
• Hypersensitivity to the active substance
• Patients with blood dyscrasias
• Pregnancy
• Breastfeeding
• Women of childbearing potential unless using effective contraceptive measures
• Patients with severe renal impairment
• Patients with severe hepatic impairment
• Colchicine should not be used in patients undergoing haemodialysis since it cannot be removed by dialysis or exchange transfusion.
• Colchicine is contraindicated in patients with renal or hepatic impairment who are taking a P-glycoprotein (P-gp) inhibitor or a strong CYP3A4 inhibitor

Warnings & Precautions
Fatal Overdose
Fatal overdoses, both accidental and intentional, have been reported in adults and children who have ingested colchicine .Should be kept out of the reach of children.

Blood Dyscrasias
Myelosuppression, leukopenia, granulocytopenia, thrombocytopenia, pancytopenia and aplastic anemia have been reported with colchicine used in therapeutic doses.

Drug Interactions
Colchicine is a P-gp and CYP3A4 substrate. Life-threatening and fatal drug interactions have been reported in patients treated with colchicine given with P-gp and strong CYP3A4 inhibitors. If treatment with a P-gp or strong CYP3A4 inhibitor is required in patients with normal renal and hepatic function, the patient's dose of colchicine may need to be reduced or interrupted. Use of Colchicine in conjunction with P-gp or strong CYP3A4 inhibitors (this includes all protease inhibitors except fosamprenavir) is contraindicated in patients with renal or hepatic impairment.

Neuromuscular Toxicity
Colchicine-induced neuromuscular toxicity and rhabdomyolysis have been reported with chronic treatment in therapeutic doses. Patients with renal dysfunction and elderly patients, even those with normal renal and hepatic function, are at increased risk. Concomitant use of atorvastatin, simvastatin, pravastatin, fluvastatin, lovastatin, gemfibrozil, fenofibrate, fenofibric acid or benzafibrate (themselves associated with myotoxicity) or cyclosporine with Colchicine may potentiate the development of myopathy. Once colchicine is stopped, the symptoms generally resolve within one week to several months.

Pregnancy
Category C
There are no adequate and well-controlled studies with colchicine capsules in pregnant women. Colchicine crosses the human placenta. Developmental studies in animals were not conducted with colchicine capsules, however published animal reproduction and development studies with colchicine demonstrated embryofetal toxicity, teratogenicity, and altered postnatal development at exposures within or above the clinical therapeutic range. Colchicine should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Nursing Mothers
Colchicine is excreted into human milk. Limited information suggests that infants exclusively breastfed receive less than 10 percent of the maternal weight-adjusted dose. While there are no published reports of adverse effects in breast-feeding infants of mothers taking colchicine, colchicine can affect gastrointestinal cell renewal and permeability. Caution should be exercised and breastfeeding infants should be observed for adverse effects when colchicine capsules is administered to a nursing woman.

Pediatric Use
Gout is rare in pediatric patients; the safety and effectiveness of colchicine capsules in pediatric patients has not been evaluated in controlled studies.

Geriatric Use
Because of the increased incidence of decreased renal function in the elderly population, and the higher incidence of other co-morbid conditions in the elderly population requiring the use of other medications, reducing the dosage of colchicine when elderly patients are treated with colchicine should be carefully considered.

Renal Impairment
No dedicated pharmacokinetic study has been conducted using colchicine capsules in patients with varying degrees of renal impairment. Colchicine is known to be excreted in urine in humans and the presence of severe renal impairment has been associated with colchicine toxicity. Urinary clearance of colchicine and its metabolites may be decreased in patients with impaired renal function. Dose reduction or alternatives should be considered for the prophylaxis of gout flares in patients with severe renal impairment. Colchicine is not effectively removed by hemodialysis. Patients who are undergoing hemodialysis should be monitored carefully for colchicine toxicity.

Hepatic Impairment
No dedicated pharmacokinetic study using colchicine capsules has been conducted in patients with varying degrees of hepatic impairment. Colchicine is known to be metabolized in humans and the presence of severe hepatic impairment has been associated with colchicine toxicity. Hepatic clearance of colchicine may be significantly reduced and plasma half-life prolonged in patients with chronic hepatic impairment.
Dose reduction or alternatives should be considered for the prophylaxis of gout flares in patients with severe hepatic impairment.

Adverse Reactions

Gastrointestinal disorders are the most common adverse reactions with colchicine. They are often the first signs of toxicity and may indicate that the colchicine dose needs to be reduced or therapy stopped. These include diarrhea, nausea, vomiting, and abdominal pain.

Colchicine has been reported to cause neuromuscular toxicity, which may present as muscle pain or weakness.

Toxic manifestations associated with colchicine include myelosuppression, disseminated intravascular coagulation, and injury to cells in the renal, hepatic, circulatory, and central nervous system. These most often occur with excessive accumulation or overdosage.

The following reactions have been reported with colchicine. These have been generally reversible by interrupting treatment or lowering the dose of colchicine:
Digestive: abdominal cramping, abdominal pain, diarrhea, lactose intolerance, nausea, vomiting

Neurological: sensory motor neuropathy

Dermatological: alopecia, maculopapular rash, purpura, rash

Hematological: leukopenia, granulocytopenia, thrombocytopenia, pancytopenia, aplastic anemia

Hepatobiliary: elevated AST, elevated ALT

Musculoskeletal: myopathy, elevated CPK, myotonia, muscle weakness, muscle pain, rhabdomyolysis

Reproductive: azoospermia, oligospermia

Drug Interactions

Colchicine is a substrate for both CYP3A4 and the transport protein P-gp. In the presence of CYP3A4 or P-gp inhibitors, the concentrations of colchicine in the blood increase. Toxicity, including fatal cases, have been reported during concurrent use of CYP3A4 or P-gp inhibitors such as macrolides (clarithromycin and erythromycin), ciclosporin, ketoconazole, itraconazole, voriconazole, HIV protease inhibitors, calcium channel blockers (verapamil and diltiazem) and disulfiram.

Colchicine is contraindicated in patients with renal or hepatic impairment who are taking a P-gp inhibitor (e.g. ciclosporin, verapamil or quinidine) or a strong CYP3A4 inhibitor (e.g. ritonavir, atazanavir, indinavir, clarithromycin, telithromycin, itraconazole or ketaconazole).

A reduction in colchicine dosage or an interruption of colchicine treatment is recommended in patients with normal renal or hepatic function if treatment with a P-gp inhibitor or strong CYP3A4 inhibitor is required .

A 4-fold reduction in colchicine dosage is recommended when co-administered with a P-gp inhibitor and/or a strong CYP3A4 inhibitor. A 2-fold reduction in colchicine dosage is recommended when co-administered with a moderate CYP3A4 inhibitor.

The magnitude of interactions with strong and moderate CYP3A4 inhibitors as well as with P-gp inhibitors from performed *in vivo* studies is summarised in the table below:

Single dose of 0.6 mg colchicine without or with:	**Number of subjects**	**% change in colchicine pharmacokinetic parameters**		**Guidance for dose reduction:**
		C_{max}	**AUC_{o-t}**	
Strong CYP3A4 inhibitors				4-fold
Clarithromycin 250 mg twice daily for 7 days	N=23	297	339	Acute gout regimen to be repeated no earlier than 3 days.
Ketoconazole 200 mg twice daily for 5 days	N=24	190	287	
Ritonavir 100 mg twice daily for 5 days	N=18	267	345	
Moderate CYP3A4 inhibitors				2-fold
Verapamil ER 240 mg once daily for 5 days	N=24	130	188	Acute gout regimen to be repeated no earlier than 3 days.
Diltiazem ER 240 mg once daily for 7 days	N=20	129	177	
Grapefruit juice 240 ml twice daily for 4 days	N=21	93	95	
Potent P-gp inhibitors				4-fold
Cyclosporin 100 mg single dose	N=23	324	317	Acute gout regimen to be repeated no earlier than 3 days.

Given the nature of the side effects, caution is advised with concomitant administration of drugs that can affect the blood count or have a negative effect on hepatic and/or renal function.

In addition, substances such as cimetidine and tolbutamide reduce metabolism of colchicine and thus plasma levels of colchicine increase.

Grapefruit juice may increase plasma levels of colchicine. Grapefruit juice should therefore not be taken together with colchicine.

Reversible malabsorption of cyanocobalamin (vitamin B12) may be induced by an altered function of the intestinal mucosa.

The risk of myopathy and rhabdomyolysis is increased by a combination of colchicine with statins, fibrates, ciclosporin or digoxin.

Dosage and Administration

Adults

Treatment of acute gout attack:

1 mg (2 tablets) to start followed by 500 micrograms (1 tablet) after 1 hour. No further tablets should be taken for 12 hours. After 12 hours, treatment can resume if necessary with a maximum dose of 500 micrograms (1 tablet) every 8 hours until symptoms are relieved.

The course of treatment should end when symptoms are relieved or when a total of 6 mg (12 tablets) has been taken. No more than 6 mg (12 tablets) should be taken as a course of treatment.
After completion of a course, another course should not be started for at least 3 days (72 hours).

Prophylaxis of gout attack during initiation of therapy with allopurinol and uricosuric drugs:

500 micrograms twice daily.
The treatment duration should be decided after factors such as flare frequency, gout duration and the presence and size of tophi have been assessed.

Patients with renal impairment:
Use with caution in patients with mild renal impairment. For patients with moderate renal impairment, reduce dose or increase interval between doses. Such patients should be carefully monitored for adverse effects of colchicine .

Clcr in mL/minute may be estimated from serum creatinine (mg/dL) determination using the following formula:

Males: $\frac{\text{(weight in kg) x (140 – age)}}{\text{(72) x serum creatinine (mg/100 mL)}}$

Females (0.85) x (above value)

Patients with hepatic impairment
Use with caution in patients with mild/moderate hepatic impairment. Such patients should be carefully monitored for adverse effects of colchicine.

Method of Administration
For oral administration. Tablets should be swallowed whole with a glass of water

Over Dosage
Colchicine has a narrow therapeutic window and is extremely toxic in overdose. Patients at particular risk of toxicity are those with renal or hepatic impairment, gastrointestinal or cardiac disease, and patients at extremes of age.

Following colchicine overdose, all patients, even in the absence of early symptoms, should be referred for immediate medical assessment.

Clinical:
Symptoms of acute overdosage may be delayed (3 hours on average): nausea, vomiting, abdominal pain, hemorrhagic gastroenteritis, volume depletion, electrolyte abnormalities, leukocytosis, hypotension in severe cases. The second phase with life threatening complications develops 24 to 72 hours after drug administration: multisystem organ dysfunction, acute renal failure, confusion, coma, ascending peripheral motor and sensory neuropathy, myocardial depression, pancytopenia, dysrhythmias, respiratory failure, consumption coagulopathy. Death is usually a result of respiratory depression and cardiovascular collapse. If the patient survives, recovery may be accompanied by rebound leukocytosis and reversible alopecia starting about one week after the initial ingestion.

Treatment:
No antidote is available.

Elimination of toxins by gastric lavage within one hour of acute poisoning.

Consider oral activated charcoal in adults who have ingested more than 0.1mg/kg bodyweight within 1 hour of presentation and in children who have ingested any amount within 1 hour of presentation.

Haemodialysis has no efficacy (high apparent distribution volume).

Close clinical and biological monitoring in hospital environment.
Symptomatic and supportive treatment: control of respiration, maintenance of blood pressure and circulation, correction of fluid and electrolytes imbalance.

The lethal dose varies widely (7-65 mg single dose) for adults but is generally about 20 mg.

Presentation
Box of 30 Tablets