

The pharmacologic basis of treatment with colchicine in children with familial Mediterranean fever

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Abstract. – Familial Mediterranean fever (FMF) is the prototype of auto-inflammatory disorders and is ethnically restricted to people living in the Mediterranean basin and Middle-East. Pyrin, the protein product of the FMF gene, expressed in myeloid cells and fibroblasts, interacts with the cytoskeletal machinery and may modulate leukocyte effector functions. At present colchicine, an alkaloid with antimetabolic activity interfering with microtubule formation, which has been used to alleviate acute gout, is the only available drug for patients with FMF to prevent both acute attacks and long-term complications such as amyloidosis. The anti-inflammatory effect of colchicine may be mediated not only through direct interaction with microtubules, but also through changes at the transcriptional level influencing cell cycle regulation and leukocyte migration. Gastrointestinal side effects may occur early and are the most frequent manifestations of colchicine toxicity in children, whilst multiple organ failure is very rarely reported as overdosage expression.

Key Words:

Colchicine, Familial Mediterranean fever, Children.

Introduction

Familial Mediterranean fever (FMF) is the name given to the most common cause of hereditary periodic fevers worldwide, an auto-inflammatory disorder frequently observed in the Mediterranean basin and Middle-East, prevalently affecting Armenians, Sephardic Jews, Turks and Arabs. The discovery of the gene causing FMF (designated *MEFV* from *MEDiterranean FeVer*) was reported independently by the French and the American consortia in 1997 and encodes for

pyrin, a protein expressed in myeloid cells, neutrophil granulocytes, monocytes, several fibroblastic cell types and physiologically involved in the regulation of inflammation and/or apoptosis pathways. The consequences of FMF-associated pyrin mutations are not still completely elucidated, but their influence upon cytoskeletal microtubules with subsequent perturbed interaction with foci of actine polymerization have been hypothesized. Colchicine is a microtubule-depolymerizing agent that has long been used to induce chromosome individualization in cells arrested at metaphase and also in the induction of polyploid plants. Since the initial Goldfinger's report in 1972 colchicine is the treatment of choice for patients with FMF¹. Primary goals of therapy in FMF is to control inflammation, ease pain and preserve organ functions, while long term-goals are to control disease activity, promote child's normal development and minimize disease impact upon the whole family. The efficacy of colchicine has been largely demonstrated in FMF and its most relevant results can be clinically observed with the daily administration for the prophylaxis of FMF typical attacks or at least in obtaining the decrease of their frequency and intensity. This drug is a polycyclic alkaloid that can be extracted from dried ripe seeds of two plants of the lily family, *Colchicum autumnale* (meadow saffron, see Figure 1) and *Gloriosa superba* (glory lily), which appears as a crystalline odourless powder darkening on exposure to light^{2,3}.

Its use as a relatively safe medication was mentioned in the first century B.C. in the treatment of acute gouty arthritis, but has been recently employed for treating an increasing number of disorders characterized by enhanced leukocyte trafficking including Behçet's syndrome, primary biliary cirrhosis, alcohol-induced

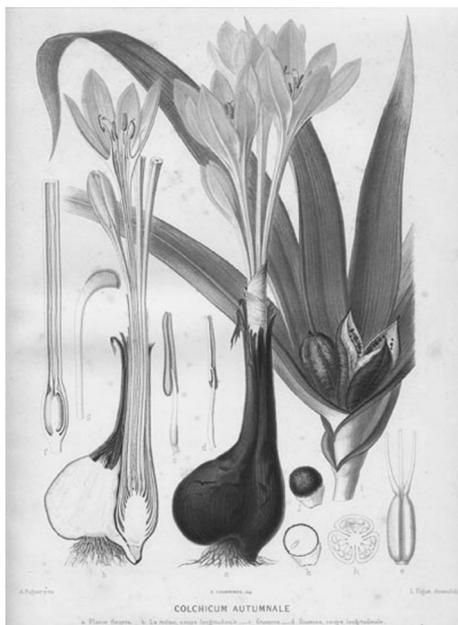


Figure 1. *Colchicum autumnale* (meadow saffron).

liver cirrhosis, psoriasis, Sweet's syndrome, scleroderma and sarcoidosis^{4,6}. Colchicine chemical structure is shown in the Figure 2.

Colchicine Absorption and Distribution

Colchicine can be administered either by mouth or intravenously. Recent studies claim that colchicine bioavailability is in the range of 25 to 50%⁷. After oral administration the time needed to reach plasma peak levels is 1 to 3 hours, with the absorption of tablets or solution showing to be similar. The exact site of intestinal absorption is unknown. After colchicine ingestion a secondary plasma peak can be registered within 6 hours of administration and this can be explained

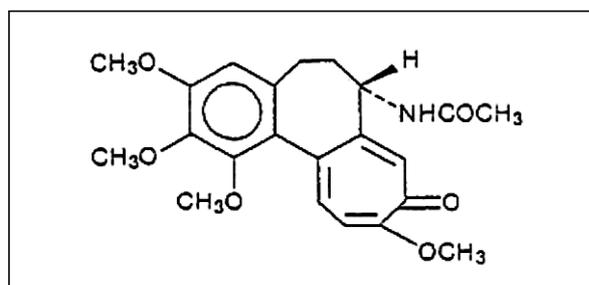


Figure 2. Chemical structure of colchicine.

by entero-hepatic circulation⁸. After intravenous administration of 2 mg colchicine a rapid drop of plasma levels occurs during the first 10 minutes followed by a logarithmic decline: the rapidity of colchicine disappearance from plasma and its persistent excretion for days suggest that it is trapped in body tissues for a long time. Furthermore it has been shown that 50% colchicine is bound to proteins in plasma. Colchicine may cross the placenta entering the foetus and appears in breast milk, though the estimated daily amount of colchicine ingested by the breast-fed neonate is less than one tenth of the therapeutic dose (per kilogram) given to the mother^{9,10}.

Colchicine Metabolism and Elimination

Colchicine is partially metabolized in the liver through deacetylation and its metabolites are excreted through the biliary tract. Renal elimination plays a less significant role with kidney responsible for the excretion of 20% unchanged colchicine. After oral ingestion of pharmacologic doses the mean half-life for elimination is 9 to 16 hours, but it may result prolonged with toxic doses. Colchicine clearance is significantly impaired in patients with kidney or liver failure: elimination half-life of colchicine conventional dosages is two-to-three-fold longer in patients with severe renal failure and even ten-fold longer in patients with renal failure and liver cirrhosis¹¹.

Colchicine Biological Effects

Colchicine activity depends on its two rings binding beta-tubulin and inhibiting the movement of intracellular granules. A host of biological functions can be theoretically influenced by colchicine such as secretion of insulin, thyroxin, amylase and catecholamines, histamine release from mast cells, discharge of lysosomal hydrolases by phagocytes, collagen transport to the extracellular space, etc. Recent studies have shown that colchicine decreases the expression of adhesion molecules on neutrophil membranes inhibiting migration and interaction with the endothelium. Other studies have shown that colchicine may modulate cytokine production from polymorphonuclear cells and prostanoid release from endothelial cells. The inhibitory effects on leukocyte functions influence their adhesiveness, ame-

booid motility, lysosome degranulation and mostly their chemotaxis. Colchicine action might be related to its concentration in leukocytes, but explanations for the special "affinity" of colchicine to white blood cells remain unclear. The anti-inflammatory effect of colchicine may be mediated not only through direct interaction with microtubules, but also through changes at the transcriptional level: this latter effect requires higher drug concentration and a longer time to occur, explaining the observation that colchicine does not have an immediate effect when given during an acute FMF attack. Because growth is the result of cell division, the effect of colchicine therapy on child development is a potential concern, though it has been demonstrated that growth under daily colchicine treatment (0.5 to 1 mg) results within the normal expected percentile range and that colchicine has to be initiated at the time of FMF diagnosis regardless of age¹².

Colchicine and Drug Interactions

Colchicine treatment alters the intestinal absorption of other compounds or orally administered medications and above all induces lactose intolerance in a significantly percentage of FMF patients compared with non-treated ones. The fact that colchicine is metabolized in the liver has raised the possibility of interaction with other molecules metabolized in the same organ. Drugs as erythromycin, cyclosporin and nifedipine compete with colchicine for their binding to liver enzymatic catabolic systems. Caution should be exercised in such cases especially when the patient also presents disturbed liver or kidney function. Colchicine intoxication has been reported when treatment was combined with macrolides such as erythromycin, josamycin and clarithromycin: thus the co-administration of colchicine and macrolides might impair colchicine elimination resulting in excess drug exposure and toxicity¹³.

Colchicine and Amyloidosis

Colchicine is of paramount importance in preventing FMF amyloidosis, but may also arrest its progression in patients who already display amyloidosis, even reversing their proteinuria. Amyloid is composed of clusters of protein strands identical to the AA protein of secondary amyloi-

dosis and infiltrates the walls of all arterioles, with the exception of central nervous system. The earliest and most consistent localization of amyloid deposition is in the kidney, where amyloidosis develops over several years and in four stages: preclinical, proteinuric, nephrotic and uremic. Before colchicine advent dialysis and kidney transplantation were the sole options used to manage this complication. Amyloidosis at any other site remains usually latent with minimal or absent symptomatology, though the prolonged survival leaves time for the clinical manifestations of amyloid deposition in extra-renal localizations to occur, such as malabsorption or potentially lethal heart failure. The daily use of colchicine for FMF attack prophylaxis and amyloidosis prevention is recommended, as well as colchicine is also recommended for treatment of the established cases of amyloidosis. Colchicine should be given to patients who have already developed amyloidosis at a dose of 2 mg/day and all patients with amyloidosis receiving a transplant kidney should continue to receive colchicine to prevent the deposition of amyloid fibrils in the graft kidneys or in other organs¹⁴.

Colchicine Side-Effects

Colchicine displays its effect by fixating the intracellular tubules and arresting their polymerization into microtubules: cell division and transport systems within the cells result disrupted. The most affected organs are those having a high cell turnover rate as gastrointestinal tract or bone marrow. Side-effect incidence increases in elder patients or in those affected by liver or kidney failure and are listed in the Table I. All adverse effects are reversible with dosage reduction or treatment interruption. As for gastrointestinal involvement the mucosal injury can induce secondary lactose intolerance with subsequent osmotic diarrhea and inhibition of Na⁺/K⁺ exchange pump regulating electrolyte transport. The elevation of serum transaminase level is frequently encountered in FMF patients during colchicine treatment, though it is not clear whether this elevation is caused by liver or muscle toxicity. Continuative therapy, even if started during childhood, has inconsistent effects on normal growth, development and fertility. Colchicine is not associated with a reduced fertility rate in women or with a higher miscarriage rate and stillbirths; on the contrary colchicine might improve female

Table I. Colchicine side-effects.

Gastrointestinal tube	Abdominal pain, nausea, vomiting, diarrhea, cholera-like gastroenteritis, abdominal distension, malabsorption syndrome, secondary lactose intolerance
Muscular apparatus	Myopathy, proximal muscular weakness, rhabdomyolysis, elevation in serum creatine kinase concentration
Peripheral nerves	Axonal neuropathy, ascending polyneuritis, hyporeflexia
Blood	Bone marrow depression (leukopenia, thrombocytopenia, aplastic anemia)
Gonads	Reversible azoospermia
Skin	Alopecia, skin reactions
Heart	Arrhythmias

fertility and pregnancy outcome¹⁵⁻¹⁷. Current policy is to recommend continuous colchicine therapy during pregnancy at a decreased dose of 0.5-1 mg/day. It remains to be determined whether FMF increases the risk of developing trisomy 21 rather than the therapy itself. Colchicine may rarely induce oligospermia or azoospermia, but some controversy exists in the evaluation of sperm production and functionality in FMF male patients. Many authors suggest that some adult sperm pathologies might be explained by the patho-physiology of FMF *per se*, such as testis amyloidosis, rather than colchicine. Rarely hypersensitivity reactions can be observed and in these cases a subsequent desensitizing treatment to colchicine (starting with initial dose of 10 µg on the first day and reaching the dose of 1 mg on the sixth day) must be performed¹⁸.

Colchicine Overdosage

Colchicine acute intoxication is rare, though associated with risk of 30% mortality: 10 mg is the toxic dose which may cause a lethal effect. First symptoms of acute toxicity occur within the first 24 hours and include nausea, vomiting, diarrhea and abdominal pain. Multi-organ failure can develop 24 to 72 hours after ingestion: bone marrow depression, hemolytic anemia, liver damage, renal failure, respiratory distress syndrome, arrhythmias, neuromuscular disturbances, paralysis and disseminated intravascular coagulation can be detected. Myo-neuropathy manifested by dis-

tal areflexia, sensory abnormalities and numbness attributable to colchicine ingestion have been anecdotally described¹⁹. Dermatologic findings as bullous lesions and painful erythema nodosum-like nodules might be related to late stages of colchicine toxicity²⁰. Overdosage may frequently lead to a cholera-like syndrome associated with dehydration, shock, acute renal failure, alopecia, hyperthermia, hepatocellular failure, epileptic seizures, coma and death. Few cases of colchicine intoxication have been reported, including pediatric reports with fatal outcome²¹⁻²⁵: the youngest patient ever-reported with colchicine intoxication was a 3-year-old child²⁶. Clinical management of colchicine toxicity can be difficult because of widespread involvement of various vital organs. Therapy is basically symptomatic and supportive. An antidotal effect of glutamate and aspartate has been reported in animal studies, whilst colchicine-specific antibodies have been shown to restore tubulin activity *in vitro*^{27,28}. Colchicine has revealed to be teratogenic in animals and there has also been suggested a risk of fetal chromosome damage in humans associated with its anti-mitotic action.

Colchicine Efficacy and Dosage

Daily colchicine is the mainstay of FMF treatment, resulting in complete remission or marked reduction in frequency, duration and severity of attacks in 85-90% patients and preventing amyloidosis, when it fails in reducing inflammatory attacks. Clinical check-up including laboratory tests should be performed regularly for monitoring disease activity and colchicine side-effects. The drug is not always effective in preventing the musculo-skeletal manifestations of FMF, namely exertional leg pains, protracted febrile myalgia or chronic protracted arthritides that might occur in about 5% patients. The percentage of non-responders to colchicine is 10-15%, but the vast majority of non-responder patients are non-compliant with the treatment or treated with insufficient dosages²⁹. In order to improve colchicine tolerance some authors recommend lactose-free diet, treatment of intestinal bacterial overgrowth and/or eradication of *Helicobacter pylori* infection. If FMF attacks result uncontrolled a higher colchicine dosage can be used for a short time (e.g. for 2-3 months): a sufficient dose results in the cessation or at least in a marked decrease of typical attacks. Colchicine dose in adults is 1 mg

daily and in non-responder patients it can be increased to 2 mg until the clinical remission is observed. In children the starting dose is adjusted according to their body weight or body surface area: the minimal dose is about 0.25 mg daily until 2 years, but the full daily dose of 1 mg can be reached at the age of 6-7. In the past it has been shown that children less than 5 years of age might need colchicine doses as high as 0.07 mg/kg/day. For a child with a body surface area superior than 1 m² the dose should be increased to the adult one. Both in patients who have developed amyloidosis and in renal failure related to amyloidosis colchicine should be given at a dose of 2 mg/day. Treatment with weekly intravenous colchicine injections (at a dose of 1 mg/week) in addition to oral colchicine therapy has revealed to be effective in patients with FMF refractory to the only oral colchicine³⁰. From this observation it can be speculated that colchicine bolus created by the intravenous administration overcomes eventual defects in drug absorption or increases serum concentration to the level required to produce pharmacological effects. It has to be reminded that colchicine extravasation might cause phlebitis, cellulitis or skin necrosis. The efficacy and side-effects of the daily single dose administration versus daily multiple doses of colchicine have been evaluated, but no difference with respect to frequency of side effects, number of attacks and acute phase response have emerged³¹. Other treatment modalities have been suggested for non-responders such as interferon-alpha, recently found to be useful in FMF prophylaxis (at the price of side effects including malaise, fever, chills, headache, nausea, myalgia and dizziness) and even in the prodromal phase of acute attacks in order to decrease their severity, biologic drugs directed towards tumour necrosis factor-alpha, particularly infliximab (at the dose of 3 mg/kg at times 0, 2, 6 weeks and then every 8 weeks) or etanercept (at the dose of 25 mg twice weekly) in patients with FMF-related amyloidosis and thalidomide (100 mg/day in association with colchicine) because of its inhibitor role in leukocyte chemotaxis and monocyte phagocytosis³²⁻³⁸. In the medical literature there is only one report of allogenic bone marrow transplantation performed in a girl with congenital dyserythropoietic anemia who also had FMF, but this procedure carries a substantial risk of transplant-related complications and mortality³⁹. Another orally active anti-fibrillary candidate for the treatment of amyloidosis and prevention of amyloid fibril for-

mation is NC-503 (or Fibrillex) due to the proven beneficial effect determined by the inhibition of amyloid-glycosaminoglycan interaction⁴⁰.

In conclusion, colchicine is actually the cornerstone in the management of FMF as it reduces the severity and frequency of attacks and is also effective in preventing FMF best-known complication which is renal amyloidosis: microtubule disruption induced by colchicine leads to short- and long-term efficacy in the prophylaxis of both acute FMF attacks and amyloidosis. Therapy must be continued all life long. The elucidation of the exact role of pyrin in the biological processes of inflammation and apoptosis will lead to a better knowledge of FMF pathogenesis and should facilitate the search for alternative molecules or the introduction of anticytokine-based therapies in the cure of FMF.

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