Colchicine in Tear Fluid of Treated Patients With Familial Mediterranean Fever

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**Purpose.** The study aimed to determine whether detectable concentrations of colchicine are present in the tear fluid of treated patients with familial Mediterranean fever (FMF) and thus demonstrate a possible route by which colchicine reaches the corneal surface. **Methods.** Tear fluid samples (50–100 μL) were collected from eight FMF patients on long-term colchicine treatment. Colchicine tear fluid concentrations were determined in all patients by radioimmunoassay using goat anticolchicine antibodies and [3H]colchicine (Dupont, Wilmington, DE). **Results.** Detectable concentrations of colchicine, with no apparent effect on the ocular surface, were found in all tear fluid samples (median, 0.46 ng/mL; range, 0.24–1.05 ng/mL). **Conclusions.** This study provides evidence of the route by which colchicine, given systemically, reaches the corneal surface and thus gives credence to the possible inhibitory effect of this drug on corneal wound healing in the cases described in the literature. **Key Words:** Familial Mediterranean fever—Peritonitis—Pleuritis—Tear fluid.

Familial Mediterranean fever (FMF) is a recessive genetic disease associated with recurrent episodes of peritonitis, pleuritis, and arthritis, which are usually associated with fever and last for 1 to 4 days. Between attacks, patients are free of symptoms and appear healthy. The disease occurs within families and is much more common in individuals of Mediterranean descent. Colchicine is an anti-inflammatory drug that is used mainly in the treatment of FMF, Behçet’s disease, rheumatoid arthritis, and primary cholangitis associated with hepatic fibrosis. It is also used clinically in an attempt to reduce fibrosis of blebs in antiglaucoma filtering surgery. Colchicine has been the drug of choice for FMF since 1972. The drug causes systemic side effects, among which gastrointestinal symptoms are the most frequent. Other less common adverse effects include bone marrow suppression, peripheral neuritis, myopathy, rash, and alopecia.

Delay of corneal wound healing in patients treated with colchicine has been reported. Experimental investigations of the effect of colchicine on the corneal wound-healing process demonstrated inhibition of fibroblast mitosis and migration, a decrease in collagen deposition, and inhibition of epithelial cell mitosis. These studies were performed in organ cultures by adding colchicine to whole rabbit corneas injured by central freezing.

The clinical reports and experimental evidence of the possible role of colchicine in the delay of corneal wound healing and the question of how the cornea is exposed to the drug prompted us to investigate whether the drug reaches the ocular surface via the film of tears.

We sought to determine whether detectable concentrations of colchicine are present in the tear fluid of patients treated with this drug.

**METHODS**

We collected tear fluid samples from FMF patients on long-term colchicine treatment. All patients were instructed to take their regular daily dose of colchicine, and at approximately 2 to 4 hours after ingestion of the drug, a single tear fluid sample of 50 to 100 μL was collected using a micropipette placed at the lower fornix. Tear fluid samples were immediately frozen at −20°C and stored in the dark. Colchicine tear fluid concentrations were determined by radioimmunoassay, using goat anticolchicine antibodies and [3H]colchicine (Dupont, Wilmington, DE) as previously described. This assay is based on colchicine-specific antibodies produced in Alpine goats immunized with different colchicine haptens conjugated to bovine serum albumin at different coupling sites on the three rings of colchicine. These antibodies exhibit a variable cross-reactivity for metabolites and structural analogs of colchicine, which are dependent on the site at which colchicine coupled to the protein carrier. The inter- and intra-assay coefficients of the assay are less than 13%. Radioactivity was counted using a Tricarb 4530 β counter (Packard, Rungis, France). The assay was designed to measure colchicine concentrations as low as 0.15 ng/mL.

This protocol was approved by the institutional review board, and all patients gave informed consent.
RESULTS

Eight patients participated in the study. All of them were on long-term colchicine treatment taking daily doses of 0.5 to 1.0 mg. We collected and analyzed their tear fluid samples. Radioimmunoassay analysis of the collected tear fluid revealed detectable concentrations of colchicine in all tear fluid samples. Patient’s characteristics and colchicine concentrations are given in Table 1.

No correlations between colchicine dose, patient age, disease duration, or the time lapse between colchicine ingestion and tear fluid sampling and the colchicine concentration in the tear fluid were found.

In all eight patients who participated in the study, there was no evidence of corneal compromise during the study period.

DISCUSSION

Since 1972, colchicine remains the treatment of choice for FMF. The adult dose is 1 mg daily, and it can be increased to 2 mg daily in nonresponsive patients. Colchicine is readily absorbed from the gastrointestinal tract and reaches peak concentration in the plasma within 1 to 3 hours. It is partially acetylated in the liver, and the unchanged drug and its metabolites are excreted in the bile and undergo intestinal reabsorption. Colchicine is found in high concentrations in leukocytes, kidneys, the liver, and spleen. Most of the drug is excreted in the feces, with 10% to 20% being excreted in the urine. The elimination half-life (T1/2) after oral ingestion is 9.3 hours. The drug is excreted in the breast milk of lactating women receiving colchicine therapy.

Colchicine is an alkaloid that may interfere with intracellular microtubule formation and function. By binding microtubules, colchicine affects mitosis and inhibits the movement of intracellular granules. It was also shown that colchicine inhibits proliferation of fibroblasts and influenced the production of interleukin-1 as well as having an inhibitory effect on leukocyte chemotaxis. Recent studies found a decrease in the expression of adhesion molecules on neutrophil membranes induced by colchicine, and inhibition of migration and interaction with endothelial cells. These biologic effects induced by colchicine may play a possible important role in cells involved in inflammation as well as in wound healing.

Colchicine is relatively weakly bound to human plasma proteins (38.9 ± 4.7%), which facilitates the diffusion of colchicine in ocular compartments. It was also found that colchicine tear fluid levels were approximately 10% to 50% of the levels normally found in the serum. Similar colchicine concentrations in tear fluid were obtained in our study.

The current study is the first to show that colchicine is also excreted in the tear fluid of patients treated systemically with the drug on a regular basis. The presumed mechanism of action of this drug and the inhibitory effect on microtubule formation and mitosis, inhibition of fibroblast proliferation, decrease in collagen deposition, and inhibition of neutrophil and endothelial cell adhesion molecules may explain the delay of corneal wound healing reported in previous studies.

In other studies performed in vitro, the colchicine concentrations used were much higher (40 ng/mL–4 μg/mL) than the concentrations found in tears of our patients (0.24–1.0 ng/mL). We cannot state whether the levels that we measured are in a toxic range because experimental inhibitory concentrations studied by others on the corneal epithelium were performed in vitro and with much higher initial colchicine concentrations.

The fact that the drug accumulates in white blood cells may cause a higher concentration of the drug in tears of inflamed eyes. However, none of the patients in the current study had an inflamed eye, and thus we could not test this theory.

Several other drugs have been investigated for their presence in tear fluid after systemic administration. One of them is amiodarone, which is known to cause corneal verticillate. This drug was shown to accumulate in the film of tears and to affect the cornea by an extrinsic route. Other drugs known to reach the corneal surface through tears are oral acyclovir, used by patients unable to tolerate topical treatment; 5-fluorouracil, which causes punctal and canalicular stenosis; and isotretinoin, a drug given systemically for acne that causes blepharoconjunctivitis and dry eye. Various other systemically given drugs, such as antibiotics, were also shown to be secreted in tears.

The present study proves the presence of colchicine in tear fluid, thus providing evidence of the possible route by which colchicine reaches the corneal surface where it may induce an inhibitory effect on corneal wound healing. In all patients who participated in our study, there was no evidence of corneal compromise during the study period. This probably means that there has to be a wound before a delay or some corneal effect is seen in patients who are treated with this drug, although larger scale experiments are needed to confirm this assumption. We believe that this information is of considerable importance for clinicians treating patients with colchicine.

REFERENCES


<table>
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<tr>
<th>Patient no.</th>
<th>Age (yr)</th>
<th>Colchicine dose/day (mg)</th>
<th>Disease duration (yr)</th>
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<th>Colchicine concentration in tears (ng/mL)</th>
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\(t_1-t_0\), the time in hours between colchicine ingestion and tear sampling.