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Original Article

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Pharmacokinetics of low doses of colchicine in the leukocytes of Japanese healthy individuals

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ABSTRACT

The venerable drug colchicine has garnered significant recent attention due to its endorsement by the United States Food and Drug Administration as an anti-inflammatory medication for cardiovascular diseases. However, the administration of this drug at its minimal available dose of 0.5 mg has been associated with certain adverse reactions. Once colchicine is administered, the drug disappears from blood in a short time and distributes in the leukocytes for a certain period of time that elicits anti-inflammatory effect. Consequently, an in-depth comprehension of the pharmacokinetics of lower dosages within leukocytes assumes important for its broader application in routine clinical contexts. In this study, we present a comprehensive analysis of the pharmacological disposition of colchicine in the plasma, polymorphonuclear leukocytes, and mononuclear leukocytes among healthy Japanese male subjects, following both single and multiple oral administrations of 0.5 mg and 0.25 mg doses of colchicine. Our investigation reveals that colchicine persists within leukocyte populations even when administered at reduced dosages. The findings herein hold promise for mitigating the adverse effects associated with its use in the treatment of inflammatory cardiovascular disorders.

Keywords: Pharmacokinetics; Leukocytes; Administration & Dosage, Colchicine

INTRODUCTION

Colchicine, an ancient Egyptian remedy for gouty joint pain [1], continues to be utilized to this day for the treatment of not only acute gout pain but also for inflammatory disorders such as familial Mediterranean fever and Behçet's syndrome. The pathogenesis of these conditions is closely linked with the activation of neutrophils or macrophages, which colchicine effectively suppresses by tightly binding to β-tubulin and disrupting the dimerization of α-β tubulin [2]. Tubulin, a critical structural component of microtubules, is responsible for the dynamic changes of polymerization and depolymerization that are

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directly involved in diverse cellular functions such as cell division, motility, exocytosis, and endocytosis [3].

Although leukocyte's activation is essential for host defence against pathogens, its excessive activation can cause harm to cells due to the release of several cytokines and reactive oxygen species, leading to organ dysfunction. The same is expected in the early stages of the infections or non-infectious atherosclerotic diseases. If the leukocyte activation serves as the initial catalyst in those clinical conditions, colchicine administration that attenuates microtubule function would be a suitable therapy.

Recent Phase III trials have demonstrated that a low dose of colchicine (0.5 mg) significantly reduces the risk of cardiovascular events [4,5], but there is a lack of clear evidence supporting the use of that dose. Currently, there are no low-dose pharmacokinetic or dose-finding studies available for colchicine. Originally developed as a short-term drug for the prevention of gout attacks, colchicine's long-term administration has only been studied in a limited number of diseases, such as familial Mediterranean fever. Although patients with coronary artery disease require long-term administration, gastrointestinal upset remains a prevalent side effect even at 0.5 mg per day, which can lead to poor adherence.

In this regard, we are now conducting some phase 2 clinical trials to investigate the effectiveness of low-dose (0.5 and 0.25 mg) colchicine in preventing cardiovascular events in Japanese patients with coronary artery disease [6], as well as in mitigating coronavirus disease 2019 aggravation in Japanese patients with mild conditions [7].

In previous studies, the distribution of colchicine in leukocytes was initially demonstrated by Wallace et al. [8] in 1970, who found that following the administration of 2 or 3 mg of colchicine, the drug was retained in leukocytes for a longer duration than in plasma. In 1993, Chappey et al. [9] demonstrates that pharmacokinetic of colchicine in plasma and leukocytes in the single or multiple administration of 1 mg of the drug using radioimmunoassay.

Although even the lowest available dose of colchicine 0.5 mg is associated with side effects such as intestinal intolerance [10], a lower dose is required for common use. However, the pharmacokinetics and disposition of lower doses of colchicine have not been studied. Toward this end, pharmacokinetic of colchicine dose titration of 0.5 and 0.25 mg by single or multiple administration was confirmed in the plasma and leukocytes in healthy Japanese men, prior to our colchicine's phase 2 clinical trials.

In addition, as the United States Food and Drug Administration (FDA) has recently approved colchicine as an anti-inflammatory drug for cardiovascular diseases, it is expected that colchicine will be prescribed to a large number of patients in the future. Therefore, our pharmacokinetic study of colchicine at doses of 0.25 mg and 0.5 mg could serve as a basis and reference for prescribing doses.

METHODS

Reagents

Colchicine tablets 0.5 mg was purchased from TAKATA SEIYAKU Co., Ltd. Some tablets are cut in halves to be 0.25 mg. Colchicine for standard solution, carbamazepine and 2-propanol

were purchased from Sigma-Aldrich (St. Louis, MO, USA). Other chemicals were obtained from FUJIFILM Wako Pure Chemical Corporation (Osaka, Japan).

Subjects and colchicine administration protocol

This study was conducted in accordance with the principles of the Declaration of Helsinki and registered on the UMIN Clinical Trial Registry (UMIN000019907). The protocols were approved by the Institutional Review Board of the University of the Ryukyus. A written informed consent was obtained from all study subjects before their enrollment.

The study targeted healthy male participants aged 18 to 40 years. Healthy individuals were recruited through advertisements within the university, excluding medical school students. Prospective candidates who applied underwent routine examinations, including physical examinations, blood and urine tests (peripheral blood count, serum protein, serum creatinine, serum sodium, potassium, liver function, serum uric acid), and electrocardiograms. Those with identified abnormalities were not be included in the study. Additionally, individuals who are continuously taking medication for any medical condition were excluded. Twenty-one Japanese healthy males (age range 19–24 years, mean ± standard deviation (SD) = 21.4 ± 1.3 years; body weight, mean ± SD = 65.2 ± 7.6 kg) were enrolled and orally administered with 0.5 or 0.25 mg of colchicine once or multiple times (for 7 days). Blood was collected after 1, 2, 4, 8, 12, 24 hours, or 0 (multiple dosage only), 1, 8, 24, 48, 96, 168 hours following the administration, as summarized in **Table 1**. The subjects in each protocol are basically administered both doses with a wash-out period of more than 2 weeks between the tests. Administration and blood collection were performed using 3 protocols to accommodate the ethical principles of blood collection to be less than 400 mL throughout the study period. The number of individual subjects was 21, and the cumulative total of 47 subjects were made by those individuals. The number of participants in each protocol were 4–12.

Isolation of plasma and leukocytes

Twenty-seven mL of blood collected via forearm intravenous canula or antecubital vein was separated into ethylenediaminetetraacetic acid (EDTA) tubes to separate plasma (7 mL) and citric acid tubes for leukocytes (20 mL) isolation. EDTA tubes were centrifuged at 1,600 g for 20 minutes at 4°C and the separated plasma was dispensed 1 mL each in microtubes. Polymorphonuclear and Mononuclear cells were isolated using Polymorphprep™ (Axis-Shield PoC AS, Oslo, Norway) following the manufacturer's protocol. Harvested cells were mixed with saline and centrifuged at 500 g for 10 minutes. The resultant pellets were suspended with 0.2–0.3 mL of saline and counted using counting chambers. All samples were stored at −30°C until the quantification of colchicine was performed.

Table 1. Summary of the protocols

Protocol	Dose	Administration	No. of participants	Sampling points after administration (hr)									
				0	1	2	4	8	12	24	48	96	168
1	0.5 mg	Single	4		✓	✓	✓	✓	✓	✓			
	0.25 mg	Single	4		✓	✓	✓	✓	✓	✓			
2	0.5 mg	Single	12		✓					✓	✓	✓	✓
	0.25 mg	Single	6		✓					✓	✓	✓	✓
3	0.5 mg	Multiple (7 days)	11	✓	✓					✓	✓	✓	✓
	0.25 mg	Multiple (7 days)	10	✓	✓					✓	✓	✓	✓

Protocols are summarized. The data of single administrations in this study are combination of Protocol 1 and Protocol 2.

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Preparation of standards and samples

Colchicine and carbamazepine were dissolved in dimethyl sulfoxide or methanol to prepare stock solutions, respectively. Stock solution of colchicine 10 mg/mL for standard were used to prepare solution of 0.01, 0.1 and 1.0 ng/mL solution. Taking out of these solutions, 0.02, 0.05, 0.1, 0.2, 0.5, 1.0, 3.0 and 9.0 ng of colchicine were dispensed into 7 mL-dark brown glass tubes to prepare standards. Sample preparation procedure was based on the method by Jiang et al. [11] with modifications. Plasma, mononuclear, and polymorphonuclear cells were thawed and each sample was transferred into a dark brown glass tube. To the colchicine standards and samples tubes, 10 ng of carbamazepine was added as the internal standard. Three mL of Mixed solvent consisting of n-Hexane:Dichloromethane:2-Propanol (300:150:15) was added to each tube, vortexed 30 seconds and shaken linearly at 240 rpm, 37°C for 30 minutes. The tubes were centrifuged at 2,000 g for 5 minutes and left in the freezer for 10 minutes to glaciate the aqueous volume. The solvent volume was decanted into 4 mL-brown glass tubes and evaporated using centrifugal evaporation devices (EYELA Tokyo Rikakikai Co. Ltd., Tokyo, Japan). One hundred mL of methanol was added to the dried-up tubes and vortexed for 1 minute to obtain samples for quantitative analysis of colchicine.

Quantitative measurement of colchicine

Colchicine concentration was determined using a Liquid Chromatograph-tandem Mass Spectrometer (LC-MS/MS) (LCMS™-8040; Shimadzu Corporation, Kyoto, Japan) by internal standard method. Liquid chromatography was done with Shim-pack FC-ODS as a column, 10 mM of ammonium formate as mobile phase A and methanol as mobile phase B, and these were provided with 0.3 mL/min of flow velocity, 10 mL of injection volume and 40°C of column temperature. Mass spectral analysis of colchicine and carbamazepine were carried out with 1.5 L/min of nebulizing gas rate, 250°C of desolvation line, 400°C of heat block temperature and electrospray ionization. The peak area ratio of colchicine and carbamazepine was utilized to evaluate the concentration of colchicine. Subsequently, concentration data of cells were converted to a concentration per unit of cell numbers. The detection limit and quantitation limit of colchicine were calculated by the supplied application to the system as 0.0035 and 0.0106 ng/mL, respectively.

Pharmacokinetic analysis

To determine pharmacokinetic parameters, non-compartmental model analysis using Phoenix WinNonlin version 8.3 (CERTARA, Princeton, NJ, USA) was performed on colchicine concentration in plasma, polymorphonuclear and mononuclear cells. The Protocol 1 and Protocol 2 were combined together to calculate the pharmacokinetic parameters for single administrations. In view of the issue of volume of blood sampling, the single administrations, in those protocols the subjects were entered both doses with wash-out period, ware divided in two protocols.

The values of maximum concentration (C_{max}) and the time to C_{max} (T_{max}) were actually measured from the observed each concentration-time profiles in the plasma, polymorphonuclear cells and mononuclear cells. The elimination rate constants were calculated by more than three time points during the elimination phase in the linear range of each concentration-time profile to obtain the half-lives ($t_{1/2}$) The area under the concentration-time curve (AUC) were determined using the trapezoidal rule. AUC_{last} is AUC from zero to the time of the last measured and $AUC_{0-\infty}$ represents the total AUC from time zero to infinity. Oral clearance (CL_F) were calculated using each dose and $AUC_{0-\infty}$.

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Because the single administrations of this study are combinations of protocol 1 and 2, each parameter could not be calculated subject-by-subject, but estimated based on the non-compartmental model as an individual using the average profile of the group instead.

RESULTS

None of the subjects presented any adverse events for the drug. Colchicine concentration in plasma, polymorphonuclear and mononuclear cells after single or multiple oral administration of 0.5 mg or 0.25 mg of colchicine are shown in **Fig. 1**. The single dose graphs are presented as combined data of the protocol 1 and 2 as represented in the **Table 1**. Colchicine pharmacokinetic parameters calculated by Phoenix WinNonlin are listed in **Table 2**.

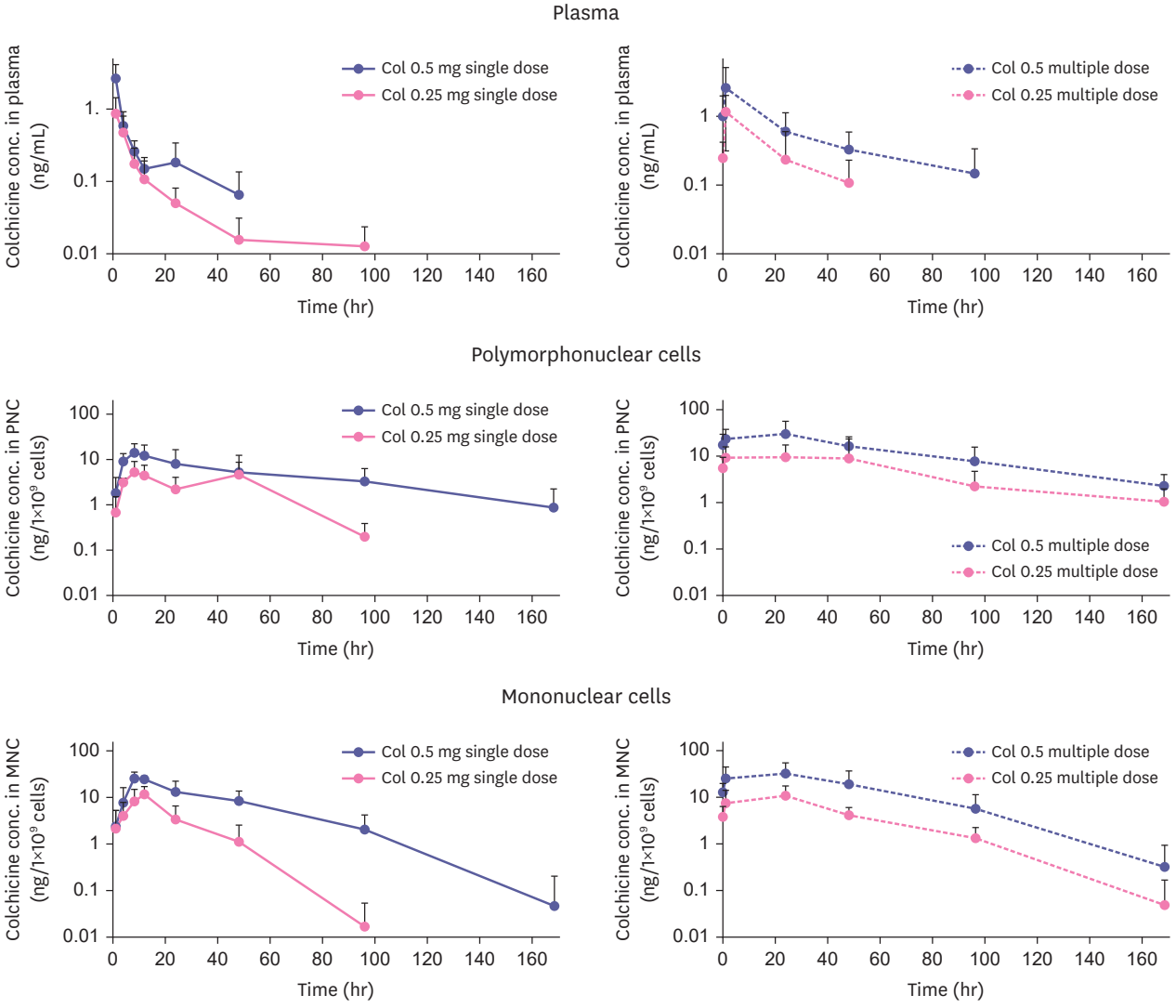

Figure 1. Concentration of colchicine in plasma and leukocytes. Colchicine concentration in plasma, polymorphonuclear and mononuclear cells after single or multiple oral administration of 0.5 mg or 0.25 mg. The data are presented as the mean ± standard deviation, and the number of participants in each group is provided in **Table 1**.
PNC, polymorphonuclear cell; MNC, mononuclear cell.

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Table 2. Colchicine's pharmacokinetic parameters from plasma, polymorphonuclear and mononuclear cells

Administration protocol	Colchicine dose			
	0.25 mg		0.5 mg	
	Single	Multiple	Single	Multiple
Plasma				
T_{max} (hr)	1	1	1	1
C_{max} (ng/mL)	0.87	1.14	2.69	2.57
$t_{1/2}$ (hr)	24.52	23.23	29.02	23.91
AUC_{last} (ng·hr/mL)	6.74	25.12	16.98	65.46
$AUC_{0-\infty}$ (ng·hr/mL)	7.20	25.22	17.28	65.75
CL_F (mL/hr)	34,736	9,911	28,928	7,605
PNC				
T_{max} (hr)	8	24	8	24
C_{max} (ng/1·10^9 cells)	5.20	9.66	13.05	30.84
$t_{1/2}$ (hr)	20.21	39.92	46.05	41.90
AUC_{last} (ng·hr/1·10^9 cells)	277	842	743	2,162
$AUC_{0-\infty}$ (ng·hr/1·10^9 cells)	283	902	801	2,301
CL_F (mg/[hr·(ng/1·10^9 cells)])	0.000884	0.000277	0.000624	0.000217
MNC				
T_{max} (hr)	12	24	8	24
C_{max} (ng/1·10^9 cells)	11.85	10.58	28.35	32.13
$t_{1/2}$ (hr)	9.13	18.32	18.87	20.06
AUC_{last} (ng·hr/1·10^9 cells)	265	570	1,009	2,110
$AUC_{0-\infty}$ (ng·hr/1·10^9 cells)	265	572	1,011	2,119
CL_F (mg/[hr·(ng/1·10^9 cells)])	0.000944	0.000437	0.000495	0.000236

Pharmacokinetics parameters of colchicine in plasma, polymorphonuclear and mononuclear cells are summarized. The data are represented as estimates calculated based on the non-compartmental model assumed the whole subjects in the group to be an individual.
T_{max}, time to C_{max}; C_{max}, maximum concentration; $t_{1/2}$, half-lives; AUC, area under the concentration-time curve; AUC_{last}, AUC from zero to the time of the last measured; $AUC_{0-\infty}$, total AUC from time zero to infinity; CL_F, oral clearance; PNC, polymorphonuclear cell; MNC, mononuclear cell.

As shown in **Figure 1**, in plasma, colchicine concentration showed maximum at 1 hour following single administration of 0.5 or 0.25 mg (mean of actual measured concentration: 2.69 ± 1.52 and 0.87 ± 0.599 ng/mL, error values represent standard deviation in this paper) and readily decreased with the terminal half-life ($t_{1/2}$), as shown in **Table 2**, for 29.02 and 24.52 hours, respectively. Colchicine was nearly undetectable from 96 hours in the single administration. In the multiple administrations, the concentration showed maximum at 1 hour after the last administration (mean of actual measured concentration: 2.57 ± 2.39 and 1.14 ± 0.824 ng/mL) with the terminal $t_{1/2}$ for 23.91 and 23.23 hours, respectively, and was not detectable at 168 hours.

Whereas in polymorphonuclear cells, the peaks appeared at longer time point than in plasma (T_{max}: 8 hours for 0.5 and 0.25 mg single administration, 24 hours for 0.5 and 0.25 mg multiple administrations). Mean colchicine concentration is described in the colchicine content per 1 × 10^9 cells. In 0.5 mg dosage, mean peak values were 13.05 ± 7.98 and 30.84 ± 26.5 ng/1 × 10^9 cells for single and multiple administrations, respectively. Similarly in 0.25 mg dosage the peaks were 5.20 ± 3.99 and 9.66 ± 7.55 ng/1 × 10^9 cells for single and multiple administrations, respectively. Terminal $t_{1/2}$ in polymorphonuclear cells of 0.5 mg single or multiple dosage ware 46.05 and 41.90 hours, those of 0.25 mg single or multiple dosage were 20.21 and 39.92 hours, respectively.

Colchicine was observed in polymorphonuclear cells at the last time point of 168 hours, except for the 0.25 mg single dosage. Similarly, in mononuclear cells, the parameters were comparable to those in polymorphonuclear cells, except for a shorter terminal half-life in every group.

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DISCUSSION

The aim of the present investigation is to elucidate the pharmacokinetics in single or multiple doses of colchicine orally administered at low doses, specifically 0.5 mg and 0.25 mg, in leukocytes and plasma of healthy volunteers. To our knowledge, no previous pharmacokinetic studies have been carried out on these low doses in leukocytes.

This study builds on the prior report by Chappey et al., [9] which examined the disposition of colchicine in plasma and leukocytes of healthy subjects after oral administration of 1 mg of colchicine, either once or multiple times for 14 days, using radioimmunoassay. Notably, our study provides novel insights through the evaluation of lower doses following single or multiple administrations, dose titration comparisons, colchicine quantitative determination using LC-MS/MS, and assessment in Japanese men.

Compared to 1 mg single dosage by Chappey et al. [9] with our single 0.5 and 0.25 mg dosage, values of C_{max} seem to be along with the dose titration in plasma, polymorphonuclear and mononuclear cells. While T_{max} values are all 1hr in every dose in plasma, shorter T_{max} in our 0.5 mg and 0.25 mg in leukocytes were shown (1 mg: 48 hours, 0.5 mg: 8 hours, 0.25 mg: 8 hours in polymorphonuclear cells. 1 mg: 48 hours, 0.5 mg: 8 hours, 0.25 mg: 12 hours in mononuclear cells). On the other hand, $t_{1/2}$ in plasma are longer in 0.5 and 0.25 mg dosage than 1 mg (1 mg: 13.5 hours, 0.5 mg: 29 hours, 0.25 mg: 24 hours). $t_{1/2}$ in leukocytes, 1 mg dosage shows longer $t_{1/2}$ in mononuclear cells than polymorphonuclear cells, while 0.5 and 0.25 mg shows longer $t_{1/2}$ in polymorphonuclear cells (1 mg: 35 hours, 0.5 mg: 46 hours, 0.25 mg: 20 hours in polymorphonuclear cells. 1 mg: 41 hours, 0.5 mg: 18.8 hours, 0.25 mg: 9.1 hours in mononuclear cells).

One potential reason for the dissimilarities in T_{max} and $t_{1/2}$ between Chappey's 1 mg and our lower dosage could be attributed to inter-ethnic disparities in drug metabolism, such as the reported loss-of-function polymorphism of CYP3A4, which is involved in colchicine metabolism, in Japanese individuals [12].

Disparities in physical characteristics, such as mean age (Chappey' 1 mg: 37.5 years, our study: 21.4 years) and mean body weight (78 kg and 65.2 kg, respectively), may have an impact on the metabolism and disposition of colchicine.

The duration of follow-up after a single administration is longer in the 1 mg dosage group (240 hours) compared to our study (168 hours). However, in the multiple dosage group, the follow-up period after the last dosage in Chappey's study (120 hours) is shorter than in our protocol (168 hours). Typically, a shorter follow-up period leads to a shorter $t_{1/2}$.

Another potential reason for the disparities could be the difference in measurement system, the radioimmunoassay in Chappey's and LC-MS/MS in ours, with the quantitation limits 0.15 ng/mL and 0.0106 ng/mL, respectively.

Since colchicine exhibits a strong binding affinity to β-tubulin (with a low dissociation constant for β-tubulin: 2×10^{-7} M [13]), many of the elimination of the drug from the body relies on the rate of cell turnover. For instance, previous studies have demonstrated that the lifespan of circulating neutrophils in humans is approximately 5.4 days [14], which aligns with our results in polymorphonuclear cells.

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Colchicine's disposition in leukocytes is preserved even though the lower doses are administered. These findings would inform some decisions on formula to reduce the adverse or side effects of colchicine on patients of inflammatory diseases.

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