Zero-order absorption and linear disposition of oral colchicine in healthy volunteers

G. Thomas 1, C. Girre 1, J. M. Scherrmann 2, P. Francheteau 3, and J. L. Steimer 3

Department of Clinical Pharmacology and 2 INSERM U26, Hôpital Fernand Widal, and 3 INSERM U194, Department of Biomathematics, Paris 6 University, Paris, France

Summary. The pharmacokinetics of colchicine has been studied in nine healthy male volunteers after oral doses of 0.5, 1, and 1.5 mg as tablets. Plasma and urine samples were collected over 48 h and analysed for colchicine by radioimmunoassay.

Individual colchicine concentration profiles in plasma and urine were well described by a two-compartment open model with zero-order input. Considering the absorption variables as specific to each experiment, the lag time (0-0.35 h) and duration (0.39-2.38 h) of absorption were found to be independent of dose, while the zero-order rate constant of absorption (k0) increased linearly with dose.

Disposition variables were taken as common to the three experiments, except in six subjects in whom renal excretion varied significantly across experiments in a dose-independent manner. For seven subjects the terminal half-life was t1/2 9.4 h, the oral apparent volume of distribution at steady-state (Vss/f) was 691 l, and the oral systemic clearance (CL/f) was 33.1 l·h⁻¹. In the two other subjects, the values were unreliable, but the estimated terminal half-life was greater than 48 h, Vss/f ranged from 1690 to 3480 l, and CL/f was in the range of the other subjects in 1 subject, and it was about 151 l·h⁻¹ in the other. In the latter subject, these estimates, together with the observation that plasma concentration reached a plateau at 2 to 5 h after ingestion, suggest enterohepatic cycling of colchicine.

Overall, the disposition of colchicine was linear in the dose range 0.5-1.5 mg, with a long terminal half-life, and absorption obeyed zero-order kinetics, with k0 proportional to dose.

Key words: colchicine; pharmacokinetics, oral administration, zero-order absorption, systemic availability, dose dependency, healthy volunteers

Colchicine has been used in the short- and long-term treatment of gout for over a century. More recently, it has become a well-accepted treatment for familial Mediterranean fever (Dinarello et al. 1974), and it has been used experimentally in an array of diseases, such as Behçet’s syndrome (Hazen and Michel 1979), scleroderma (Alarcon-Segovia et al. 1979), pustulosis palmaris et plantaris (Takigawa et al. 1982), and cirrhosis of the liver (Kaplan et al. 1986; Kershenobich et al. 1988).

Whereas colchicine is usually given orally on a long-term basis, most available pharmacokinetic data come from following colchicine concentrations for periods of time of less than 3 h after its intravenous administration. Using radiolabelled colchicine Wallace et al. (1970) estimated a plasma elimination half-life of 9 to 40 min in four groups of patients with gout, renal disease, liver disease and miscellaneous disorders. The same investigators subsequently developed a radioimmunoassay and found a half-life of 58 min in patients free from hepatic and renal disease (Ertel et al. 1976). In healthy subjects Halkin et al. (1980) calculated a mean elimination half-life of 65 min.

However two sources of data indicate that, due to their short periods of follow-up, these studies did not characterize the elimination phase. First, Ertel et al. (1969), working with leukocytes in vitro, noted that the short plasma half-life of colchicine was not explained by its elimination from the body, but rather by its distribution to the tissues. Second, in some subjects colchicine could be detected in plasma up to 7 days and in urine up to 10 days after the intravenous administration of 2 mg (Ertel et al. 1976).

In the only systematic oral study, Wallace and Ertel (1973) monitored plasma concentrations of colchicine for 48 h after the oral administration of radiolabelled colchicine to ten healthy volunteers, but they did not report either the terminal half-life or the apparent volume of distribution. They noted only that the handling of colchicine by the digestive tract was complex and that it needed further examination.

Due to the well-known dose-dependent toxicity and low therapeutic index of colchicine, it would be desirable to base therapeutic regimens on pharmacokinetic data. This led to the present investigation of the pharmacokinetics of colchicine in healthy volunteers after oral administration.
Materials and methods

Subjects and dosage forms

The study was approved by the Ethics Committee of the hospital. Nine healthy male volunteers, after giving their written informed consent, took colchicine orally, at weekly intervals, in doses of 0.5, 1, and 1.5 mg, according to a randomized cross-over design.

The volunteers were 25.5 years old (range 20 to 27 years), had a mean weight of 68.1 kg (range 62 to 78 kg). Colchicine was given in the form of commerically available tablets and as a 0.5 mg tablet specially prepared for the study by Houdé-ISH.

Urine was collected over the periods 0-2, 2-4, 4-6, 6-8, 8-10, 10-24, and 24-48 h. The volume of each sample was measured and 10 ml aliquots were stored in the dark at -20°C until assayed.

Analysis of plasma and urine

Colchicine concentrations were determined by the radioimmunoassay of Scherrmann et al. (1980). The intraassay coefficient of variation was 6 to 8%, the interassay coefficient of variation was 5 to 13%, the accuracy was 83 to 110%, and the sensitivity was 0.05 μg·L⁻¹. Several metabolites of colchicine were assayed for cross-reactivity at concentrations of 1 to 10 μg·L⁻¹, namely 2-demethylcolchicine, 3-demethylcolchicine, colchicine, and N-deacetylcolchicine. They yielded apparent colchicine concentrations of less than 0.05 μg·L⁻¹.

Pharmacokinetic calculations

Plasma and urine concentration data for colchicine were fitted by a two-compartment open model with zero-order input (Fig. 1). First-order absorption was rejected because of a systematic fitting bias, with the corresponding model underestimating the peak in all instances.

The differential equations of the model are:

\[ \frac{dA_1}{dt} = k_0 - (k_{12} + k_e + k_{NR}) \cdot A_1 + k_{21} \cdot A_2 \]

with \( k_0 = 0 \) for \( t < t_{lag} \) or \( t > t_{end} \)

\[ \frac{dA_2}{dt} = -k_{21} \cdot A_2 + k_{12} \cdot A_1 \]

\[ \frac{dA_e}{dt} = k_e \cdot A_1 \]

\[ C = f \cdot A_1 / V_c \]

Where:

- \( A_1 \) and \( A_2 \) are the amounts in the central and peripheral compartments, respectively.
- \( A_e \) is the amount eliminated from the central compartment.
- \( C \) is the concentration in plasma.
- \( f \) is the fraction available to the systemic circulation.
- \( V_c \) is the volume of the central compartment.

The rates of urinary excretion of colchicine were calculated at the mid-points of the collection intervals by dividing the amount excreted by the duration of the interval. The fraction excreted unchanged was calculated as: \( k_e / (k_{NR} + k_e) \).

We define:

- the oral apparent volume of the central compartment \( V_c / f \).
- the oral apparent volume of distribution at steady-state \( V_{ss} / f = (1 + k_{12} / k_{21}) \cdot V_c / f \).
- the oral systemic clearance \( CL / f = (k_{NR} + k_e) \cdot V_c / f \).

Data analysis

The model was fitted simultaneously to the three sets of dose data from each subject. Absorption variables (\( V_c / f, t_{lag}, t_{end}, k_0 \)) were considered specific for each experiment and disposition variables (\( k_{12}, k_{21}, k_{NR}, k_e \)) were considered constant across experiments. However, in six subjects the constraint on \( k_e \) was released, because it produced a prediction bias for the urinary data.

The model was fitted to the data by the non-linear regression program PHACIN (Vilain et al. 1988), using variable step-size integration for the differential equations, and extended least squares analysis for data fitting. The data were weighted according to the following model for the error variance:

\[ V = a^2 + b^2 \cdot S^2 \]

where \( S \) is the predicted concentration in plasma or urine, \( a \) is 0.05 μg·L⁻¹, and 0.01 μg·L⁻¹, and \( b \) is 0.05 and 0.15 for plasma and urine data, respectively.

Comparison of the absorption variables and of \( k_e \) across doses was done by Friedman's two-way analysis of variance. The dependence of \( k_e \) on dose was evaluated by analysis of covariance. The tests were carried out with programs 2V and 3S of the BMDP Statistical Software (Dixon et al. 1985).

The models were compared by the likelihood ratio test.