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Pharmacokinetics and absolute bioavailability of colchicine after i. v. and oral administration in healthy human volunteers and elderly subjects

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Abstract. The pharmacokinetics of colchicine were studied in six healthy male and four elderly female volunteers after i. v. and oral administration. Plasma samples were collected over 72 h and assayed for colchicine by a specific and sensitive radioimmunoassay. Plasma concentration-time curves were fitted using a three-compartmental model after i. v. administration of 0.5 mg (healthy volunteers) and 1 mg (elderly group) colchicine. The first distribution half-life ($t_{1/2}\,\lambda_1$) was short: 9.2 min in healthy volunteers and 3.0 min in the elderly group; the second distribution half-life ($t_{1/2}\,\lambda_2$) was of the same order for both groups, 1.2 h. Plasma elimination half-lives were also in the same range: 30 h for healthy volunteers versus 34 h for the elderly subjects. Mean residence time was also in the same range in the two groups: 27 h in healthy volunteers and 21 h for elderly subjects. The volume of distribution (V_z) was 6.7 $l \cdot kg^{-1}$ for the healthy group and 6.3 $l \cdot kg^{-1}$ for the elderly group, while V_{SS} was smaller: 4.2 $l \cdot kg^{-1}$ for healthy volunteers and 2.9 $l \cdot kg^{-1}$ for elderly subjects. Total body clearance was 10.5 $l \cdot h^{-1}$ for healthy and 5.5 $l \cdot h^{-1}$ for elderly subjects.

After oral administration of 1 mg, lag-time was 14 min in healthy volunteers and 11 min in elderly subjects. Maximal plasma concentration was 5.5 $ng \cdot ml^{-1}$ at 62 min in the healthy group, while in the elderly group C_{max} was 12 $ng \cdot ml^{-1}$ at 87 min. Mean absolute bioavailability of the tablet was the same in both groups, 44 % for healthy volunteers and 45 % for elderly subjects.

Key words: Colchicine; pharmacokinetics, healthy volunteers, elderly subjects, absolute bioavailability

Colchicine is the reference drug for treating acute as well as long-term gout [1]. It has also been used to treat familial Mediterranean fever [2], Behçet's syndrome [3], scleroderma [4], pustulosis palmaris and plantaris [5], and liver cirrhosis [6]. Toxicity during colchicine therapy is frequent and renal or hepatic failure is known to increase the risks of toxicity [7].

Despite awareness of the low therapeutic index of colchicine, little has been done until recently to study its pharmacokinetics, largely due to the lack of suitable sampling protocols and analytical methods for estimation of colchicine in body fluids.

In 1976, Ertel et al. [8] and Halkin et al. [9] performed pharmacokinetic studies in humans and described the mean elimination half-life as 60 min. In 1979, Galliot et al. [10] using a fluorimetric method reported an elimination half-life of 548 min in urine. Finally, Scherrmann et al. [11] developed a sensitive radioimmunoassay and found detectable levels of colchicine over 48 h after oral administration of 1 mg.

Using the same analytical procedure, Thomas et al. [12] studied the pharmacokinetics of colchicine in nine healthy male volunteers after oral doses of 0.5, 1 and 1.5 mg as tablets. Plasma colchicine disposition was well described by a two-compartment open model with zero-order input.

In this paper we extend Thomas et al.'s work by investigating the pharmacokinetics of colchicine in healthy and elderly volunteers after oral and i. v. administration. This allows calculation of absolute colchicine bioavailability for the first time and determination of colchicine disposition using i. v. bolus data.

Materials and methods

Subjects

The study was approved by the ethics commitees of the René Muret and Fernand Widal hospitals.

Healthy volunteers. After giving informed consent, six healthy male volunteers received at 2-week intervals 0.5 mg i. v. colchicine and a 1-mg colchicine tablet, according to a randomized, cross-over design. Mean age was 24 years (range 23–25 years), mean weight was 68 kg (range 61–80) and mean creatinine clearance was 94 $ml \cdot min^{-1}$ (range 81–98).

Elderly subjects. Four elderly females received an i. v. bolus of 1 mg colchicine. After a washout period of 2 weeks they took one tablet of

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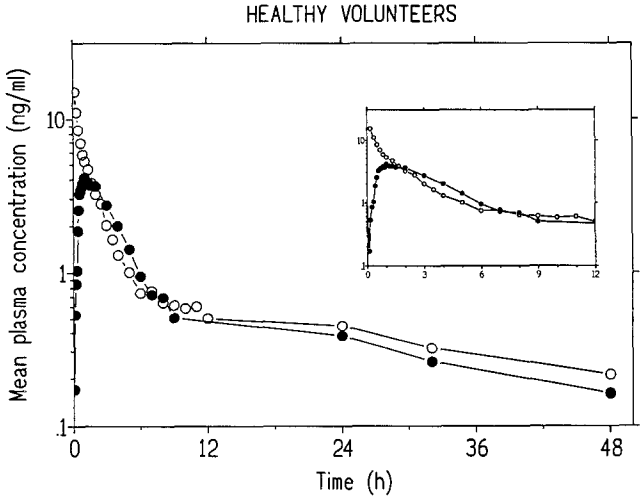

Fig. 1. Mean plasma concentration-time curves for the i. v. and oral doses in healthy subjects. ○ IV route; ● Oral route

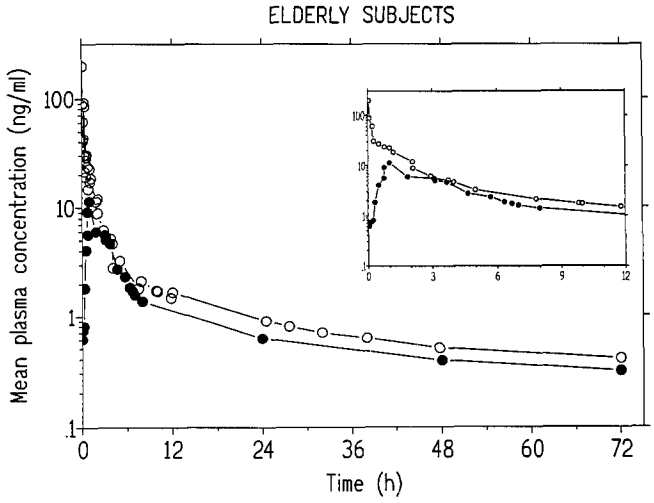

Fig. 2. Mean plasma concentration-time curves for the i. v. and oral doses in elderly subjects. ○ IV route; ● Oral route

1 mg colchicine. Mean age was 83 years (range 75–93), mean weight was 47 kg (range 38–61), and mean creatinine clearance was 46 ml · min^{-1} (range 25–75).

Colchicine was administered orally as 1-mg tablets (Houdé-Ish, Paris, France) and i. v. as an injectable solution at 1 mg · ml^{-1} (Houdé-Ish).

Blood sampling

Plasma samples were collected before ingestion and at 5, 10, 15, 20, 25, 30, 35, 40, 45, 50, 55, 60, 70, 80 and 90 min and then 2, 3, 4, 5, 6, 7, 8, 9, 24, 32 and 48 h after oral administration of a 1 mg colchicine tablet. After i. v. administration samples were taken at 2, 7, 10, 20, 30, 40, 50, 60, 80, 100 and 120 min and then 2.5, 3, 3.5, 4, 5, 6, 7, 8, 9, 10, 11, 12, 24, 32 and 48 h. For the elderly group, plasma samples were collected up to 72 h. Samples were immediately centrifuged and stored in the dark at –20 °C until assayed.

Drug analysis

Colchicine concentrations were determined by the radioimmunoassay method of Scherrmann et al. [11]. The intra-assay coefficient of variation was 6–8 %, the interassay coefficient of variation 5–13 %, the recovery 83–110 % and the limit of detection 0.15 ng · ml^{-1}. Several colchicine metabolites were assayed for cross-reactivity at concentrations of 1–10 ng · ml^{-1}, namely 2-demethylcolchicine, 3-demethylcolchicine, colchiceine, and *N*-deacethylcolchicine. They yielded apparent colchicine concentrations of less than 0.05 ng · ml^{-1}.

Pharmacokinetic calculations

IV route. Using the model previously described by Thomas et al. [12], plasma concentration data were fitted by a three-compartment mammillary model where drug administration, measurement and elimination occurred exclusively through the central compartment. Distribution ($t_{1/2}\,\lambda_1$, $t_{1/2}\,\lambda_2$) and elimination half-lives ($t_{1/2}\,\lambda_z$) were estimated from the semilogarithmic plasma drug concentration-time curve. AUC was calculated by the linear trapezoidal rule and corrected for the residual area extrapolating to infinity by dividing the last measured drug concentration by λ_z; mean residence time $\bar{t}$ was determined by dividing AUMC by AUC, where AUMC is the area of the first statistical moment curve; total body clearance (CL) was calculated by dividing ingested dose by AUC; apparent volume distribution in the λ_z phase (V_z) by dividing CL by λ_z; volume of distribution at steady state was defined as follows:

$$V_{SS} = \frac{D \times AUMC}{(AUC)^2}$$

$$= V_c + V_2 + V_3$$

$$= (1 + \frac{k_{12}}{k_{21}} + \frac{k_{13}}{k_{31}})V_c$$

where V_c, V_2 and V_3 are respectively volumes of the central and the two peripheral compartments; and k_{12}, k_{13}, k_{21} and k_{31} (in units of reciprocal time) are intercompartmental rate constants.

Oral route. For the oral route, maximum plasma concentration (C_{max}) and time to C_{max} (t_{max}) were taken directly from the observed data. Lag-time (t_{lag}) was measured directly from the experimental data.

The absolute bioavailability f of the tablet formulation was calculated using:

$$f = \frac{AUC_{p.o.} \times D_{IV} \times (t_{1/2}\lambda_z)_{IV}}{AUC_{IV} \times D_{p.o.} \times (t_{1/2}\lambda_z)_{p.o.}}$$

The most commonly applied method for bioavailability assessment is based on the assumption that total body clearance of the individual remains unchanged from one test dose to another administered on a separate occasion. However, as there were intraindividual variations, correction by half-lives was used [13].

Data analysis

The model was fitted to the data by the nonlinear regression program SIPHAR (Simed, Créteil, France) using weighted least-squares analysis for data fitting. In order to assess the goodness of fit, residual analysis (an examination of the standard deviation) was performed. In addition to the likelihood ratio test, Akaike, Leonard and Schwarz criteria were tested to select the most appropriate model [14]. Calculated pharmacokinetic parameters obtained for healthy volunteers and elderly subjects were tested statistically to detect significant differences between the two groups. A *t*-test was applied for variables with a Gaussian distribution, whereas the Mann-Whitney test was used for variables with a non-Gaussian distribution. *P* values were calculated on raw data; the significance level was set at $P < 0.05$.

Table 1. Pharmacokinetic parameters in the healthy and elderly volunteers

	Healthy Volunteers i.v. dose 0.5 mg		Elderly Subjects i.v. dose 1 mg	
Parameters	Mean ± (SD)	(range)	Mean ± (SD)	(range)
$t_{1/2}\lambda_1$ (min)	9.2 ± (3.9)	(3–14)	3.0 ± (1.6)**	(1.8–5.7)
$t_{1/2}\lambda_2$ (h)	1.2 ± (0.2)	(0.9–1.4)	1.2 ± (0.1)*	(1.1–1.3)
$t_{1/2}\lambda_z$ (h)	30 ± (6.0)	(23–41)	34 ± (8.0)*	(21–41)
AUC (ng · ml · h)	48 ± (6.1)	(36–54)	186 ± (23)**	(154–217)
$\bar{t}$ (h)	27 ± (7.0)	(18–39)	21 ± (11)*	(10.5–35)
V_z (l · kg)$^{-1}$	6.7 ± (1.4)	(5.0–8.5)	6.3 ± (2.3)*	(2.3–8.1)
V_{SS} (l · kg)$^{-1}$	4.2 ± (0.9)	(3.2–5.6)	2.9 ± (1.7)*	(1.2–5.2)
CL (l · kg)$^{-1}$	10.5 ± (1.5)	(9.2–13.7)	5.5 ± (0.7)**	(4.6–6.5)
Vc (l)	19 ± (6.8)	(11–29)	2.4 ± (1.4)**	(1.3–4.7)
V_2 (l)	19 ± (3.8)	(11–23)	12 ± (7.8)*	(3.1–24)
V_3 (l)	252 ± (62)	(184–348)	117 ± (59)**	(54–178)
k_{12} (h)$^{-1}$	2.7 ± (2.2)	(0.9–7.2)	11 ± (5.8)**	(17–2.2)
k_{21} (h)$^{-1}$	2.1 ± (0.8)	(1.3–3.8)	2.0 ± (0.9)*	(0.9–3.3)
k_{13} (h)$^{-1}$	0.9 ± (0.3)	(0.5–1.5)	2.1 ± (0.9)**	(0.8–3.2)
k_{31} (h)$^{-1}$	0.06 ± (0.01)	(0.05–0.09)	0.04 ± (0.01)**	(0.02–0.05)
k_{10} (h)$^{-1}$	0.6 ± (0.2)	(0.4–0.9)	3.1 ± (1.1)**	(1.4–4.0)
	Oral dose 1 mg			
t_{lag} (min)	14 ± (5)	(5–20)	11 ± (4)*	(4–15)
C_{max} (ng · ml)$^{-1}$	5.5 ± (1.4)	(4.0–7.6)	12 ± (4)**	(6.0–17)
t_{max} (min)	62 ± (30)	(35–120)	87 ± (28)*	(60–120)
f (%)	44 ± (17)	(18–66)	45 ± (19)*	(33–79)

A *t*-test was applied for variables to detect significant differences between the two groups (significance level was set at $P < 0.05$) (for t_{max},, the Mann-Whitney test was applied). * Non significant; ** significant

Results

The mean plasma concentration-time curves for the i.v. and oral doses for healthy and elderly subjects are shown in Figs. 1 and 2, respectively. Mean pharmacokinetic parameters are given in Table 1. Plasma concentration-time curves were all fitted using a three-compartment model after i.v. administration of colchicine. Plasma concentrations were higher in elderly subjects. Total area under the plasma curve was four times smaller in healthy volunteers than in elderly subjects, who therefore received twice the dose: 48 (6.1) ng · ml^{-1} · h vs 186 (23) ng · ml^{-1} · h. The first distribution process was three times faster in the elderly group than in healthy volunteers [$t_{1/2}\lambda_1$ = 3.0 (1.6) and 9.2 (3.9) min, respectively, $P = 0.0272$]; colchicine distributed more rapidly from the central compartment in the elderly group [k_{12} was four times greater: 11 (5.8) h^{-1} vs 2.7 (2.2) h^{-1}, $P = 0.0247$] because it distributes in a smaller volume [V_c is eight times smaller in the elderly group: 2.4 (1.4) l, vs 19 (6.8) l, $P = 0.023$]. The second distribution phase (λ_2 term) lasted 7 h in the two groups, the volume of distribution V_2 was also similar [19 (3.8) l and 12 (7.8) l, $P = 0.1533$]. Thus, colchicine distributed from this compartment at the same rate in both the elderly and young groups [k_{21}, 2.0 (0.9) h^{-1} and 2.1 (0.8) h^{-1}, respectively, $P = 0.81$]. The volume of distribution in the deep compartment, V_3 was 2-fold higher in the healthy volunteer group [252 (62) l vs 117 (59) l, $P = 0.016$]. The rate of elimination from this deep compartment (k_{31}) was as low in the elderly as in healthy volunteers [0.04 (0.01) h^{-1} vs 0.06 (0.01) h^{-1}]. Plasma elimination half-lives were also in the same range: 30 (6) h for healthy volunteers vs 34 (8) h for the elderly subjects. Mean residence time was also in the same range in the two groups: 27 (7.0) h in healthy volunteers and 21 (11) h for elderly subjects. The volume of distribution (V_z) was about 6.7 (1.4) l · kg^{-1} for the healthy group and 6.3 (2.3) l · kg^{-1} for the elderly group, while V_{SS} was calculated by a model-independent method and was found to be higher in healthy volunteers [4.2 (0.9) l · kg^{-1} vs 2.9 (1.7) l · kg^{-1}, $P = 0.20$]. Total body clearance was two times higher in healthy volunteers than in elderly subjects [10.5 (1.5) l · h^{-1} vs 5.5 (0.7) l · h^{-1}, $P < 0.001$].

After oral administration of 1 mg of colchicine in the two groups, the lag-time was 14 (5) min in healthy volunteers and 11 (4) min in elderly subjects. Maximal plasma concentrations were two times higher in elderly subjects [12 (4) ng · ml^{-1} at 87 (28) min] than in healthy volunteers [5.5 (1.4) ng · ml^{-1} at 62 (30) min, $P = 0.018$]. Mean absolute bioavailability of tablets was similar in the two groups: 44 (17) % for healthy volunteers and 45 (19) % for elderly subjects ($P = 0.930$).

Discussion

Until recently, analytical methods were not sensitive enough to study colchicine pharmacokinetics at therapeutic doses because of the low plasma levels. The detection limit of high performance liquid chromatography techniques is above 5 ng · ml^{-1} and the application of these procedures is limited to toxicological detection in cases of acute poisoning [15]. Specific radioimmunoassays (RIAs) for plasma and urine colchicine have been developed with substantial improvement in sensitivity [8, 9]. Using these RIA techniques, the first pharmacokinetic studies showed an elimination half-life of 60 min [8, 9]. Recently, the phar-

macokinetics of colchicine were again investigated using a polyclonal antiserum-based RIA procedure with a low detection limit (0.25 ng · ml^{-1}) and a high specificity for colchicine [11]. The antiserum does not cross-react with 2- and 3-demethylated metabolites of colchicine which have been isolated after incubation with rat liver microsomes [11].

As colchicine pharmacokinetics were previously demonstrated to be linear between doses of 0.5 to 1.5 mg [16], 0.5 or 1 mg colchicine doses were used in the study allowing the measurement of plasma colchicine up to 72 h. Using the model-dependent approach of Thomas et al. [12], the plasma time-course of colchicine following i. v. infusion can be fitted by a three-compartment open model in healthy and elderly groups. The first distribution phase occurs very quickly after i. v. administration and lasts a few minutes and is never observed after oral administration; this phenomenon of vanishing exponential terms is common after extravascular administration and was first described by Wagner et al. [17]. This also explains the magnitude of the plasma concentrations and AUC values measured in V_c, because muscular mass is reduced in the elderly (mean weight 68 kg vs 47 kg). Distribution in the deep compartment was very intensive: V_3 accounts for about 90 % of the total volume of distribution both in healthy volunteers and in elderly subjects. This was higher than the total extracellular fluid volume.

This compartment model, which depicts the pharmacokinetics of colchicine for the first time, is a good tool for analysing differences in the disposition processes in healthy volunteers and elderly subjects. As renal clearance contributes only 10% of total body clearance [16], physiological changes in renal clearance in the elderly are not sufficient to significantly alter total body clearance; but decrease in hepatic clearance, since biliary excretion is the major route of colchicine excretion, could explain the lower clearance in elderly subjects. A decrease in both CL and V_{SS} of the same order in the elderly group explains the similar plasma terminal half-lives in the two groups. Plasma terminal half-lives of unchanged colchicine after i. v. administration, whatever the initial dose, was similar for the two groups, about 25–40 h. These values agree with those recently described by Thomas et al. [12] and Girre et al. [16], allowing for the greater sensitivity of our assay which permitted the analysis of drug levels throughout the 48 h post-ingestion period.

After oral administration of a 1-mg tablet, colchicine was rapidly absorbed from the gastrointestinal tract. The latent period of absorption ranged from 10 to 15 min in the two groups, corresponding to the lag-time found by Thomas et al. [12] of about 10 min in nine healthy male volunteers. Maximal plasma concentrations found in our study for healthy volunteers are in good agreement with those determined by Achtert et al. [18] for the same oral dose in 12 healthy volunteers [4.15 (2.35) ng · ml^{-1}]. Therefore, higher peak plasma colchicine concentrations were observed in elderly subjects despite the absolute bioavailability of colchicine in tablet form being about 45 % in both groups. This could be explained by lower distribution volume in central and peripheral compartments and reduced total body clearance for the elderly increasing plasma colchicine concentrations in comparison to healthy volunteers. Simultaneous analysis of oral and i. v. data allowed absolute bioavailability to be calculated for the first time and was found to be 45 % (20) % in both groups, which reflects high variability.

In conclusion, colchicine absorption is similar in healthy volunteers and elderly subjects. However, decreases in distribution and total body clearance in the elderly advises close monitoring of colchicine dosage in elderly subjects.

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