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Technical note

Pharmacokinetics and bioavailability of pentoxifylline in healthy volunteers-a comparative study of three oral formulations

Milena Pokrajac [a,*], Branislava Miljković [a], Dragan Simić [b], Branka Brzaković [a], Aleksandra Galetin [a]

[a] *Department of Pharmacokinetics, Faculty of Pharmacy, Vojvode Stepe 450, 11000 Belgrade, Yugoslavia*
[b] *Clinical Centre 'Dr Dragiša Mišović', Belgrade, Yugoslavia*

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1. Introduction

Pentoxifylline (1-(5-oxohexyl)-3,7-dimethyl-xanthine) is used in the treatment of intermittent claudication or other circulatory disorders. Its hemorrheologic effects include reducing blood viscosity and increasing erythrocyte deformability.

Pentoxifylline given orally is rapidly and extensively absorbed, with peak plasma levels reached between 0.29 and 0.41 h after dosing. Pentoxifylline is converted to several renally excreted metabolites, and $< 1\%$ of the dose is recovered unchanged from the urine. Extensive metabolic transformations are responsible for the low and variable bioavailability of the drug. Plasma clearance varies from 1.3 to 1.8 ml/min. In healthy volunteers, the drug is eliminated from the body with a short half-life, of 1–2 h [1–3]. A sustained-release 400 mg tablet is currently available commercially, which allows a patient to reduce dosing frequency while maintaining therapeutic plasma concentrations.

The study was undertaken to compare single-dose bioavailability in healthy volunteers of novel oral pentoxifylline formulations, relative to a marketed formulation.

2. Materials and methods

2.1. Formulations

Test formulations:	Pentoksifilin film-coated tablets, Slaviamed, Belgrade, Yugoslavia-T_1 Pentoksifilin dragees, ICN-Galenika, Belgrade, Yugoslavia-T_2
Reference formulation:	Trental® 400 dragees, Jugoremedija, Zrenjanin, Yugoslavia-R

2.2. Subjects

The investigation was performed on 12 healthy male subjects, aged from 26 to 40 years (33 ± 3; mean $\pm$ S.D.) and of mean body mass 77 ± 15 kg, ranging from 62 to 109 kg. Before entering the study, volunteers had a routine physical examination and were subjected to a set of laboratory tests, which were found to be normal. All subjects gave in writing their informed consents, after the study had been approved by the local ethics committee.

2.3. The study design

The comparative pharmacokinetic and bioavailability study of three oral pentoxifylline formulations was

* Corresponding author. Department of Pharmacokinetics, Faculty of Pharmacy, Vojvode Stepe 450, P.O. Box 146, 11000 Belgrade, Yugoslavia.

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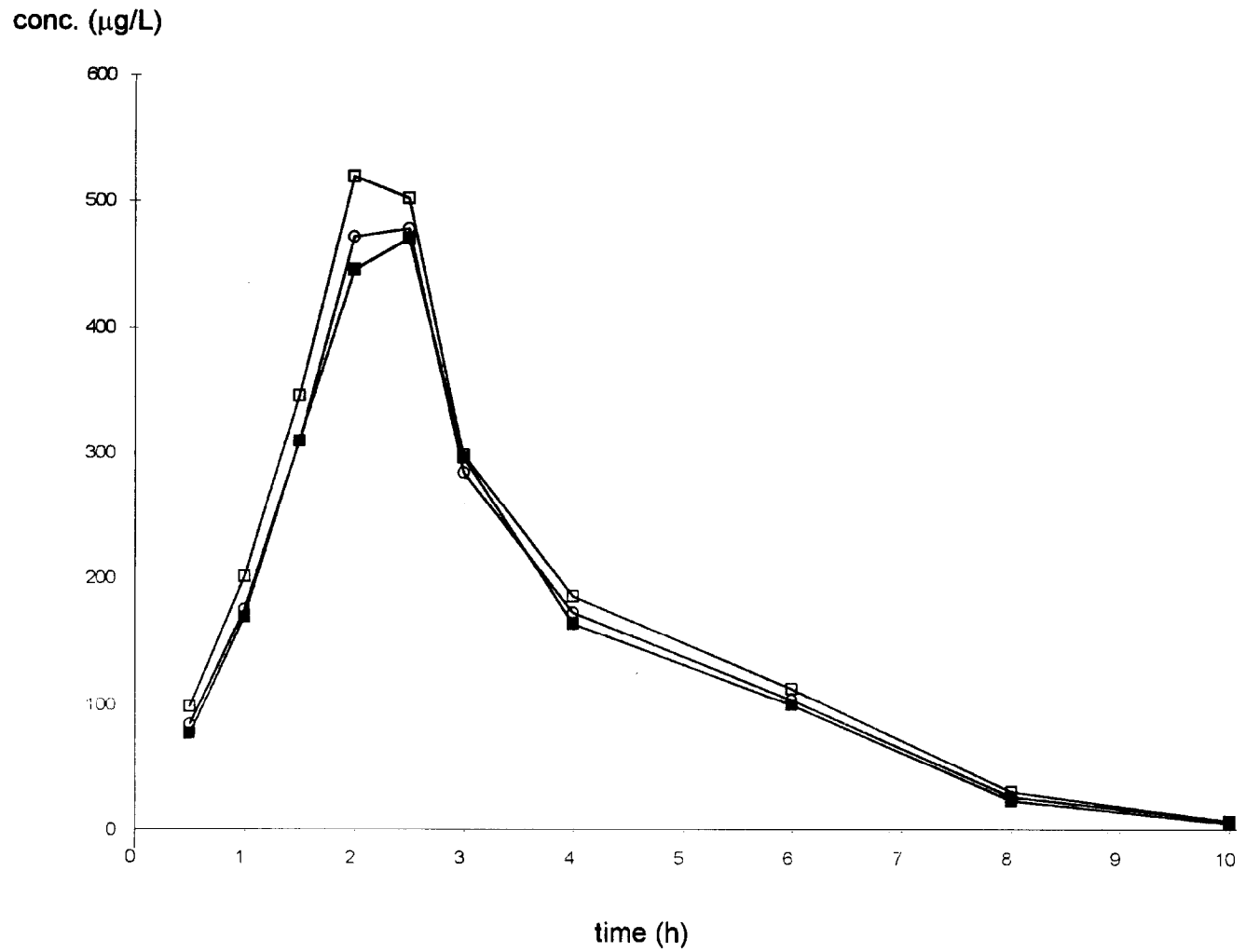

Fig. 1. Mean plasma concentrations of pentoxifylline in 12 healthy volunteers, after single oral administration (400 mg) of three pentoxifylline formulations: trental®400 dragees (■), pentoksifilin film-coated tablets (○), and pentoksifilin dragees (□).

carried out as an open randomized three-way crossover investigation in which the two test formulations: film-coated tablets and dragees (T_1 and T_2), were compared with one reference formulation-dragees of pentoxifylline (R).

Test and reference formulations were administered as single oral doses of 400 mg after an overnight fast, and 4 h before a standardized breakfast. Blood was collected in heparinized tubes prior to the drug administration-zero time, and at 0.5, 1, 1.5, 2, 2.5, 3, 4, 6, 8 and 10 h afterwards. Plasma samples were stored at −20°C until analyzed. An interval of 7 days was a washout period between investigations with the same subject.

2.4. Analytical procedure

Pentoxifylline plasma concentrations were determined in our study by a slightly modified HPLC procedure previously described [4].

To prepare the sample for analysis, 100 μl of 1 mol/l sodium hydroxide and 5 ml of dichloromethane were added to 1 ml of plasma. The mixture was vortexed and centrifuged. The upper aqueous layer was removed by aspiration. The organic layer was placed in another test tube and evaporated to dryness. The residue was reconstituted in 100 μl of mobile phase (water-methanol; 55:45, v/v) and a 20 μl-aliquot was injected onto the column. The liquid chromatograph (Hewlett Packard series 1050, Avondale, PA) was equipped with a diode-array UV detector set at 273 nm and separation was achieved using a C_{18} reversed-phase column (Hypersil ODS, 5 μm, 200 × 4.6 mm) with a C_{18} guard column. The analysis was carried out at ambient temperature with a flow rate of 1.5 ml/min.

The analytical procedure described had a limit of detection of 5 μg/l, linearity from 10 to 800 μg/l, and no endogenous/exogenous interference. Recoveries of the drug were high (about 96%). The accuracy data, documented by the coefficients of variation-CV (within-

Table 1
Mean values of pharmacokinetic parameters of pentoxifylline for Trental 400 dragees (R), Pentoksifilin film V-coated tablets (T_1) and Pentoksifilin dragees (T_2)

Pharmacokinetic parameters		Mean ± S.D.	CV (%)
C_{max} (μg/l)	R	541 ± 91	16.8
	T_1	584 ± 120	20.5
	T_2	628 ± 102	16.2
t_{max} (h)	R	2.3 ± 0.3	13.1
	T_1	2.3 ± 0.3	13.1
	T_2	2.2 ± 0.3	13.6
β (1/h)	R	0.5291 ± 0.0409	14.6
	T_1	0.5061 ± 0.0321	6.3
	T_2	0.5042 ± 0.0425	8.4
$t1/2$ β (h)	R	1.32 ± 0.09	6.8
	T_1	1.37 ± 0.08	5.8
	T_2	1.38 ± 0.11	8.0
Cl (l/h/kg)	R	3.8 ± 1.0	26.3
	T_1	3.7 ± 0.9	24.3
	T_2	3.4 ± 0.7	20.6
V_d (l/kg)	R	7.3 ± 2.0	27.4
	T_1	7.4 ± 2.0	27.0
	T_2	6.8 ± 1.5	22.1
AUC 0–10 (μgh/l)	R	1407 ± 229	16.3
	T_1	1451 ± 272	18.7
	T_2	1578 ± 259	16.4
AUC 0–oo (μgh/l)	R	1422 ± 231	16.2
	T_1	1471 ± 277	18.8
	T_2	1600 ± 263	16.4

day CV < 7%, day-to-day < 10%) showed the high reproducibility of the method.

3. Pharmacokinetic calculations and statistics

Pharmacokinetic calculations and statistics were performed with programs PHARM/PCS Version 4.0 TRS-80 Model III, Pharmacologic Calculation System (C), 1986, R.B. Murray and Biotest Program, 1990, M. Olling, respectively. Maximum plasma concentrations (C_{max}) and the time to peak (t_{max}) were taken directly from the concentration-time curves. The trapezoidal rule was used for the determination of the area under the pentoxifylline plasma concentration-time curve from $t = 0$ up to the last measured data point ($AUC_{0\rightarrow t}$). The terminal elimination rate constant (β) was computed by linear regression analysis over the terminal data points showing a linear trend in a semi-log plot. To extrapolate $AUC_{t\rightarrow\infty}$, the value of the last measured pentoxifylline concentration was divided by β. Total clearance (Cl) was obtained for each subject when the dose of pentoxifillyne (400 mg) was divided by $AUC_{0\text{-}\infty}$, and the volume of distribution (V_d) was obtained through division of clearance by β [5–7].

Statistical tests used for comparative bioavailability assessments (T_1 and T_2 vs. R preparation) were Westlake 90% confidence intervals, Fluehler posterior probabilities and Nonparametric tests [8–10]. The comparison of T_1 formulation with T_2 formulation of pentoxifylline employed Student's t-test (paired data) and ANOVA (three sources of variation). The pharmacokinetic parameters were log-transformed before ANOVA.

4. Results and discussion

The mean plasma pentoxifylline concentrations in 12 volunteers, measured throughout 10 h after the administration of three pentoxifylline formulations are shown in Fig. 1. The similarity of concentration-time profiles for the investigated formulations is illustrated by this figure.

Pharmacokinetic parameters (C_{max}, t_{max}, β, $t_{1/2\beta}$, Cl, V_d, $AUC_{0\rightarrow 10}$, $AUC_{0\rightarrow\infty}$) are calculated individually on the basis of concentration-time data. From individual pharmacokinetic parameters, their mean values (± S.D.) were obtained and are shown in Table 1 for both test (T_1 and T_2), as well as for the reference formulation of pentoxifylline (R). The mean plasma levels peaked from 541 to 628 μg/l at on the average 2.3 h post dose. After absorption and distribution, plasma pentoxi-

Table 2
The statistical analysis of the pharmacokinetics and bioavailability of pentoxifylline from three different formulations (T_1-pentoksifilin film V-coated tablets, T_2-pentoksifilin dragees, and R-trental 400 dragees)

		Westlake's test (%)	Non-parametric probability test
C_{max}	T_1 vs. R	82–118	0.94–1.20
	T_2 vs. R	82–118	1.14–1.19
t_{max}	T_1 vs. R	87–113	0.82–1.12
	T_2 vs. R	89–111	0.89–1.00
AUC 0–oo	T_1 vs. R	81–119	0.87–1.20
	T_2 vs. R	83–117	1.07–1.19
		ANOVA	Student's t-test
C_{max}, t_{max}, β, $t_{1/2}\beta$, Cl, V_d, AUC 0–10, AUC 0-oo	T_1 vs. T_2	NS	NS

fylline concentrations declined with elimination half-life of 1.1–1.5 h for both test ($T_1$and T_2) and reference (R) formulations.

Table 2 presents the results of the statistical analysis of pharmacokinetic parameters of pentoxifylline. There were no significant differences neither in the values of the pharmacokinetic parameters necessary for bioavailability characterization (C_{max}, t_{max}, $AUC_{0\rightarrow\infty}$) between test (T_1 and T_2) and reference formulations of pentoxifylline (R), nor between the two investigated test formulations (T_1 and T_2). In addition, there were no significant differences in the values of other parameters (β, $t_{1/2\beta}$, Cl, V_d) calculated to completely define the pharmacokinetic properties of pentoxifylline in the evaluated oral formulations.

The results of the statistical comparison between the test (T_1 and T_2) pentoxifylline preparations (Table 2) demonstrated the absence of significant differences in the values of calculated parameters, and, consequently, very similar pharmacokinetic profiles of pentoxifylline in both tested formulations.

The results obtained made it possible to conclude that both test oral formulations of pentoxifylline (pentoksifilin film-coated tablets, T_1 and pentoksifilin dragees, T_2) may be considered bioequivalent to the reference preparation (TRENTAL® 400 dragees).

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