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Pharmacokinetics and Bioavailability of Tranexamic Acid

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Summary. Tranexamic acid 1 g was given intravenously to three healthy volunteers. Plasma concentrations decayed in three monoexponential phases. Most elimination took place during the first eight hours, giving an apparent elimination half-life of approximately two hours. Plasma clearance ranged between 110–116 ml/min. The urinary recovery of tranexamic acid exceeded 95% of the dose. Ten healthy volunteers were given tranexamic acid 2 g orally on an empty stomach, and together with a meal. Food had no influence on the absorption of tranexamic acid, as judged by comparison of the peak plasma concentration, the time required to reach the peak, the AUC from zero to six hours, and the urinary excretion data. The oral bioavailability of tranexamic acid, calculated from 24 h urinary excretion after oral and intravenous administration, was 34% of the dose.

Key words: tranexamic acid; pharmacokinetics, bioavailability, oral absorption, influence of food, plasma clearance

Tranexamic acid has been in clinical use for several years in the treatment of various fibrinolytic disorders. The drug is used orally and intravenously. The pharmacokinetics of tranexamic acid after intravenous administration was reported by Eriksson et al. (1974). With their analytical procedure, the blood concentrations of tranexamic acid after a one gram dose could only be followed for eight hours. The development of an assay based on electron capture gas chromatography after derivatization made it possible to study blood concentrations for up to 32 h after a single intravenous dose.

The blood concentrations reported by Eriksson et al. (1974) could be described by a two-term exponential equation, but the urinary excretion indicated that a third exponential term was required to accurately describe the data. The aim of the present paper is to describe the blood concentrations of tranexamic acid observed after intravenous and oral administration, and to report on the bioavailability of tranexamic acid after oral administration, when the drug was given with food and on an empty stomach.

Material and Methods

Dosage Forms

Cyklokapron® (Kabi AB, Sweden) solution for injection, 0.1 g/ml. Batch No. 91643. Titrimetric assay 96 mg/g. Specific gravity 1.03 g/ml. Amount per ampoule 10.7 g.

Cyklokapron® (Kabi AB, Sweden) tablets 0.5 g. Batch No. 90288. Assay 499 mg/tablet.

Design of Experiment

Intravenous Study. Three healthy male volunteers took part in the study. They had no history of gastrointestinal, liver or kidney disease. Their clinical laboratory data were normal (Table 1), and their health was verified by a physician.

The subjects were not allowed to take any drugs during the week preceding the study, and were instructed to fast from 10 p. m. on the night prior to the experiment. The dose was given at 8 a. m. and lunch was served after 3.5 h. Subsequently, the subjects took their ordinary meals. The first three hours of the experiment were carried out at a hospital ward.

Tranexamic acid 1 g was administered intravenously over five minutes, with a constant rate, by a syringe. The amounts of tranexamic acid remaining in the syringe and in the emptied ampoule were assayed, and the net amount injected was calculated.

Venous blood samples were collected in 10 ml heparinized Vacutainers® (Becton, Dickinson & Co.,

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Table 1. Clinical and laboratory data for the volunteers participating in the intravenous study

Subject	Weight [kg]	Height [cm]	Age [years]	ESR [mm]	Hb [g/l]	WBC	Serum creatinine [μmol/l]	Urine volume [l/24 h]	Endogenous creatinine clearance [ml/min]	S-$ZnSO_4$ arb. units	Urine sugar	Urine protein	ASAT [μkat/l]	ALAT [μkat/l]
L. L.	66	168	39	6	140	6000	71	0.88	127	3.7	neg	trace	0.19	0.17
O. E.	80	176	43	15	144	8000	97	0.95	121	4.2	neg	trace	0.25	0.38
S. N.	73	174	36	4	157	6000	74	1.18	121	2.7	neg	neg	0.26	0.55
Reference values of the analytical laboratory				< 20	130–165		<130		80–160	< 8			< 0.70	< 0.70

Table 2. Plasma concentration of tranexamic acid after intravenous administration of one gram at a constant rate over 5 min. Times after the start of the injection

Subject L. L.		Subject O. E.		Subject S. N.	
Time	Plasma concentration, [mg/l]	Time	Plasma concentration, [mg/l]	Time	Plasma concentration, [mg/l]
10 min	86.0	10 min	86.0	10 min	81.8
20 min	61.0	20 min	65.6	20 min	63.8
30 min	49.0	33.5 min	47.1	30 min	44.4
1 h	31.0	1 h	32.3	1 h	31.7
1.5 h	25.1	1.5 h	25.9	1.5 h	25.0
2 h	20.5	2 h	17.4	2 h	20.8
3 h	14.4	3 h	12.0	3 h	13.0
4 h	9.0	4 h	7.6	4 h	9.3
7 h	5.1	7 h	3.3	7 h	4.0
9.5 h	2.3	9.5 h	2.2	9.5 h	2.1
12 h	0.91	12 h	1.3	12 h	1.3
24 h	0.27	24 h	0.45	24 h	0.30
30 h	0.22	30 h	0.26	30 h	0.23
32 h	0.22	32 h	0.25	32 h	0.22

Rutherford, N. J., USA) immediately before dosing and approximately 10, 20 and 30 min, and 1, 1.5, 2, 3, 4, 7, 9.5, 12, 24, 30 and 32 h after the start of the injection (exact times are given in Table 2). Plasma was separated by centrifugation and was stored at −20 °C until assayed. Urine was collected quantitatively in fractions for 72 h in tared polyethylene containers. Immediately before the administration, and at the end of each collection period, the subject emptied his bladder. A zero time specimen was kept as a blank. Samples were collected for the time periods given in Table 3. After weighing, aliquots were stored at −20 °C until assayed.

Oral Study. Ten healthy male volunteers participated in the study. Their health was verified as above. The subjects were not allowed to take any drugs for one week prior to the study or during the study. They fasted for nine hours before each experiment.

One group of five subjects was given tranexamic acid 2 g (four Cyklokapron tablets 0.5 g) with 100 ml water. They continued to fast for further three hours when a standardized meal was served. The meal consisted of one egg, one roll of white bread, butter, cheese and coffee or tea. An other group of subjects ate same meal supplemented with two slices of bacon, fried potatoes and milk 0.3 l. Immediately after the meal, each subject took four Cyklokapron tablets 0.5 g with 100 ml water. Lunch was served to both groups six hours after the dose. Venous blood samples were collected in heparinized Vacutainers before the dose and 0.5, 1, 1.5, 2, 3, 4, 5 and 6 h after it. Plasma was separated and treated as above. Urine was collected for 24 h. Five subjects collected urine for 48 h.

One week later the groups were 'crossed over' to the other treatment.

Determination of Tranexamic Acid in Plasma and Urine

The analyses of plasma and urine samples were done by electron capture gas chromatography after derivatization, according to Vessman and Strömberg (1977). At a plasma level of 12 mg/l the method showed a relative standard deviation of ± 1.4% (n = 8), and at a level of 0.24 mg/l, requiring a thin layer chromatographic clean up, the relative standard deviation was ± 7% (n = 8).

Pharmacokinetics

Intravenous. The plasma concentration time curves after intravenous administration showed three monoexponential phases. The experimental plasma concentration-time data were fitted to an equation containing three exponential terms (Eq. 1), where Cp denotes plasma concentration. C_1–C_3, α, β and γ are

Table 3. Urinary excretion of tranexamic acid in three healthy male volunteers after intravenous administration of one gram

Subject	Collection period [h]	Volume of urine [ml]	Amount excreted [mg]	Excretion rate [mg/h]	Cumulative excretion [% of dose]
L. L.	0– 2	96	652	326	64.6
[dose: 1010 mg]	2– 4	65	151	75.7	79.6
	4– 6	56	66.8	33.4	86.2
	6– 8	78	38.9	19.5	90.0
	8–10	104	26.0	13.0	92.6
	10–12	101	10.6	5.30	93.7
	12–24	274	19.3	1.61	95.6
	24–30	320	6.40	1.07	96.2
	30–48	695	9.52	0.529	97.1
	48–54	403	1.9	0.32	97.3
	54–72	825	3.0	0.17	97.6
	0–72		986		
O. E.	0– 2	205	369	185	36.7
[dose: 1007 mg]	2– 4	295	417	209	78.1
	4– 6	172	85.8	42.9	86.6
	6– 8	284	43.5	21.7	90.9
	8–10	187	24.1	12.1	93.3
	10–12	442	16.8	8.38	95.0
	12–24	630	22.9	1.91	97.3
	24–30	581	4.9	0.81	97.8
	30–48	900	4.5	0.25	98.2
	48–54	190	1.1	0.19	98.3
	54–72	480	0.77	0.043	98.4
	0–72		991		
S. N.	0– 2	88	622	311	62.2
[dose: 1000 mg]	2– 4	55	137	68.6	76.0
	4– 6	64	79.9	39.9	83.9
	6– 8	71	39.4	19.7	87.9
	8–10	81	22.4	11.2	90.1
	10–12	400	sample lost		
	12–24	562	34.9	2.91	> 93.6
	24–30	222	5.37	0.895	> 94.2
	30–48	501	6.31	0.351	> 94.8
	48–54	261	0.81	0.13	> 94.9
	54–72	420	1.6	0.089	> 95.0
	0–72		> 950		

constants and t_{post} is the time after the end of the injection period.

$$C_p = C_1 \cdot e^{-\alpha \cdot t_{post}} + C_2 \cdot e^{-\beta \cdot t_{post}} + C_3 \cdot e^{-\gamma \cdot t_{post}} \quad (1)$$

The curve fitting was done using the nonlinear regression program NONLIN (Metzler et al. 1974) on an IBM 370/155 digital computer, with weights equal to one, 1/Cp and $1/Cp^2$. The best fit was obtained using weights equal to 1/Cp. The fitting was done with time zero equal to the end of the five minute injection period. The values of the mixed rate constants α, β and γ (Table 4) indicated that the short injection period could not be neglected in the calculations. In order to convert Eq. (1) to the form commonly used for describing plasma concentration time data obtained after rapid intravenous administration (Eq. 2), the coefficients C_1, C_2 and C_3 were converted to A, B and C using equations 3–5 (Niazi 1976; Wagner et al. 1977),

$$Cp = A \cdot e^{-\alpha t} + B \cdot e^{-\beta t} + C \cdot e^{-\gamma t} \quad (2)$$

$$A = \frac{C_1 \cdot \alpha \cdot \tau}{1 - e^{-\alpha\tau}};\ B = \frac{C_2 \cdot \beta \cdot \tau}{1 - e^{-\beta\tau}};\ C = \frac{C_3 \cdot \gamma \cdot \tau}{1 - e^{-\gamma\tau}} \quad (3\text{–}5)$$

where τ is the time of the constant injection.

Plasma concentrations during the injection were calculated according to Eq. (6)

$$C_p = \frac{R_{inj}}{V_1}\left[\frac{A'}{\alpha}(1 - e^{-\alpha t_{inj}}) + \frac{B'}{\beta}(1 - e^{-\beta t_{inj}}) + \frac{C'}{\gamma}(1 - e^{-\gamma t_{inj}})\right] \quad (6)$$

Table 4. Parameter estimates from non-linear regression fitting of plasma concentrations to Eq. (1), calculated parameters and parameter estimates from urinary excretion data

	Subject					
	L. L.		O. E.		S. N.	
Parameter	Estimate	SD	Estimate	SD	Estimate	SD
$\alpha[h^{-1}]$	3.42	12.3%	3.74	11.9%	4.10	13.6%
$\beta[h^{-1}]$	0.334	5.73%	0.591	5.69%	0.445	6.45%
$\gamma[h^{-1}]$	0.0280	27.2%	0.0970	11.0%	0.0947	13.6%
C_1[mg/l]	64.6	6.93%	52.1	7.91%	57.2	8.75%
C_2[mg/l]	37.3	6.11%	45.8	6.95%	40.2	7.36%
C_3[mg/l]	0.508	20.2%	4.69	13.6%	3.57	19.2%
A[mg/l]	74.3		60.7		67.5	
B[mg/l]	37.8		46.9		41.0	
C[mg/l]	0.508		4.71		3.58	
V_1[l]	8.97		8.96		8.92	
AUC[mg/l·h]	153		144		146	
Plasma clearance [ml/min]	110		116		114	
From urinary excretion data						
$\beta[h^{-1}]$	0.37		0.33		0.37	
$\gamma[h^{-1}]$	0.050		0.079		0.077	

where R_{inj} is the rate of injection, V_1 is the initial dilution space equal to dose/(A+B+C) and A', B' and C' are the relative coefficients (A' = A/(A+B+C) etc.). t_{inj} is the time during the injection.

After the end of the injection Eq. (1) was used.

If the renal elimination of tranexamic acid were a linear function of the plasma concentration, a plot of urinary excretion rate versus the midpoint of the sampling time interval should give a curve of the same shape as the plasma concentration-time curve. Because of its short duration, the first exponential decay in plasma concentration was not expected to appear in the urinary excretion rate curve. The mixed rate constants β and γ were calculated from a semi-logarithmic plot of urinary excretion rate versus time by the feathering technique.

The overall plasma clearance was calculated as dose/AUC, where AUC, the area under the plasma concentration-time curve, was taken as $(A/\alpha + B/\beta + C/\gamma)$. For tranexamic acid, the overall renal clearance was equal to the overall plasma clearance, since almost 100% of the dose was recovered in urine as intact drug.

Oral. The systemic bioavailability of tranexamic acid after oral administration was calculated as the mean amount of tranexamic acid excreted in the urine in 24 h after its oral administration (10 subjects) divided by the mean amount excreted in urine in 24 h after its intravenous administration (3 subjects).

Further, approximate measure of systemic bioavailability was calculated by comparing the mean AUC after oral and intravenous administration. The AUC from zero to six hours after oral administration was calculated by the trapezoidal rule. The residual area was calculated assuming a monoexponential final decay with a half-life of 2 h.

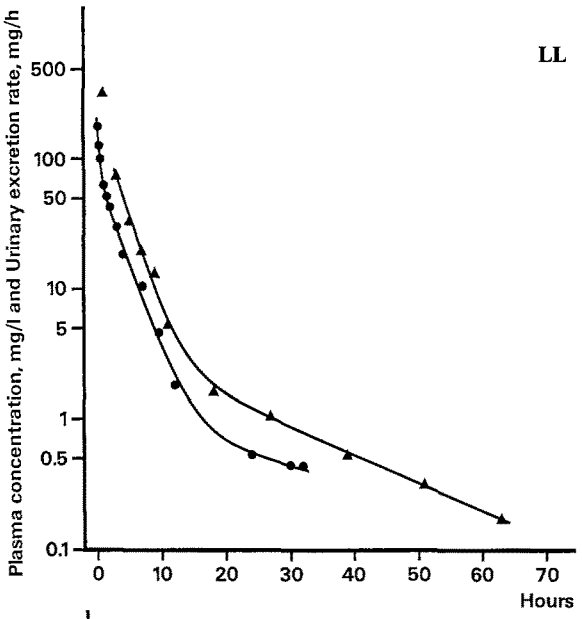
The mean renal clearance was calculated as the mean urinary excretion in 24 h divided by the extrapolated AUC.

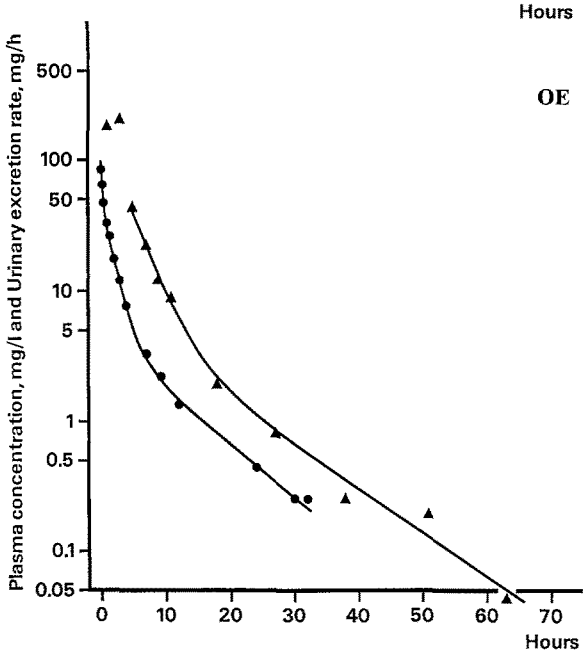
The influence of food on the oral bioavailability of tranexamic acid was studied by comparing (paired t-test) the maximum plasma concentration, the time required to reach the maximum concentration, the amount excreted in urine in 24 h and the AUC from zero to six hours between treatments.

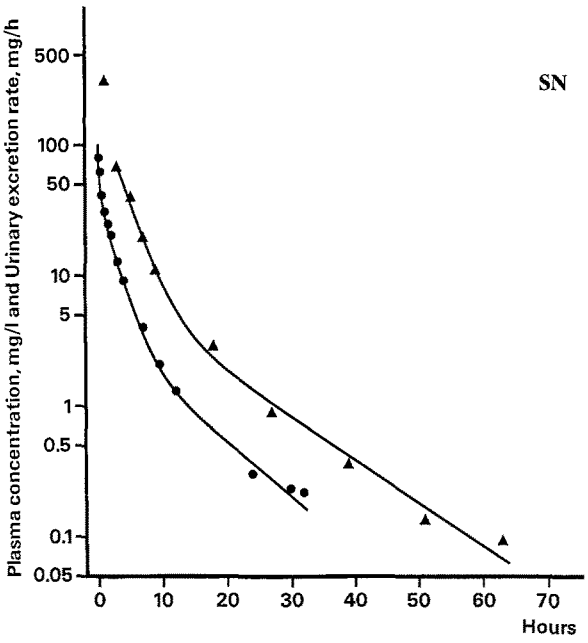
Results

Intravenous Study

The results of the plasma and urine analyses after intravenous administration are given in Tables 2 and 3. The total amount of tranexamic acid excreted in urine in 72 h, 97.6%, 98.4% and > 95% of the dose







Figs. 1–3. Plasma concentration of tranexamic acid versus time, and urinary excretion rate of tranexamic acid versus t_{mid} (midpoint of the sampling time interval) for subjects L. L., O. E. and S. N. after a single intravenous dose of 1 g. ● = experimental plasma concentrations. The solid curves are calculated from Eq. 1 using parameter estimates given in Table 4. ▲ = experimental urinary excretion rates. The solid curves are calculated from $219 \cdot e^{-0.37 t_{mid}} + 3.98 \cdot e^{-0.050 t_{mid}}$ (L. L.), $185 \cdot e^{-0.33 t_{mid}} + 7.24 \cdot e^{-0.079 t_{mid}}$ (O. E.) and $198 \cdot e^{-0.37 t_{mid}} + 8.64 \cdot e^{-0.077 t_{mid}}$ (S. N.), respectively

for subjects L. L., O. E. and S. N., respectively, shows that urinary excretion is the main route of elimination.

In the curve fitting of plasma concentration-time data three different weighting functions were used. The best fit, judged by the magnitude of the asymptotic standard deviations of the parameters, by the correlation coefficients and by the randomness of scatter of the weighted residuals (Boxenbaum et al. 1974), was obtained with weights equal to 1/Cp. The results of the curve fitting are given in Table 4, in which it can be seen that the parameters associated with the first two exponential phases were estimated with reasonable accuracy, while C_3 and γ show a greater standard deviation. The variation between subjects was small. The experimental results and the calculated curves are shown in Figs. 1–3.

The initial dilution space (volume of the central compartment) was close to 9 l and the overall plasma clearance was 110 to 116 ml/min (Table 4).

The urinary excretion rate curves are also shown in Figs. 1–3. Estimates of β and γ obtained by the feathering technique are given in Table 4. β and γ from urinary excretion rate determinations were of the same magnitude as those obtained by fitting the plasma concentrations. Since only three plasma sam-

Table 5. Plasma concentration, AUC and urinary excretion after oral administration of tranexamic acid 2 g together with food and under fasting conditions. Plasma concentration in mg/l. Urinary excretion in mg. AUC in mg/l × h

Subject No.	Plasma concentration, hours after administration									Urinary excretion		AUC
	0	0.5	1	1.5	2	3	4	5	6	0–24 h	0–48 h	0–6 h
Fasting conditions												
1	0	4.0	11.4	14.1	16.4	15.4	12.6	8.5	6.1	715	741	66.6
2	0	3.4	10.3	14.7	17.7	16.4	12.8	8.0	3.2	765	780	66.3
3	0	2.1	9.1	9.7	9.3	9.1	6.9	5.5	4.2	471	491	41.0
4	0	6.4	13.3	15.8	15.6	17.9	14.5	10.9	7.4	664	684	76.5
5	0	0.5	4.6	9.1	10.5	12.4	12.0	9.5	6.3	580	596	52.0
6	0	3.0	8.6	10.5	11.8	15.7	12.4	10.9	7.7	732		62.8
7	0	3.9	7.1	8.6	9.3	10.1	8.2	6.7	4.4	424		44.0
8	0	1.3	5.5	8.8	12.3	13.1	15.2	12.3	7.7	538		61.5
9	0	2.3	7.7	12.6	15.4	16.3	14.9	9.6	7.4	775		67.4
10	0	2.2	6.1	10.2	12.2	12.4	10.7	10.4	9.3	726		56.6
Mean		2.9	8.4	11.4	13.1	13.9	12.0	9.2	6.4	639		59.5
SD		1.6	2.7	2.7	3.0	2.9	2.8	2.1	1.9	127		11.1
With food												
1	0	1.6	7.6	11.4	12.8	12.2	9.1	6.7	4.6	568		50.2
2	0	3.1	8.6	13.7	17.7	21.7	17.9	13.3	9.1	751		83.4
3	0	0.5	3.4	8.2	11.6	15.8	14.5	12.4	10.8	770		62.9
4	0	0	7.8	16.0	18.9	19.6	18.7	15.2	10.7	635		84.9
5	0	1.5	6.7	12.8	13.0	11.8	9.1	6.7	5.1	420		50.4
6	0	1.7	7.8	12.0	14.1	15.2	14.7	13.7	11.9	946		70.9
7	0	0.8	4.6	9.8	12.2	16.2	15.4	13.0	9.3	790		66.0
8	0	0.5	2.7	6.1	9.1	11.8	12.0	11.6	9.5	582		51.6
9	0	1.8	5.7	9.1	9.7	9.5	7.6	5.7	3.4	517		40.1
10	0	1.7	4.0	6.9	8.7	11.6	11.9	11.5	9.0	712		52.3
Mean		1.3	5.9	10.6	12.8	14.5	13.1	11.0	8.3	669		61.3
SD		0.9	2.1	3.1	3.4	3.9	3.8	3.4	2.9	154		15.0

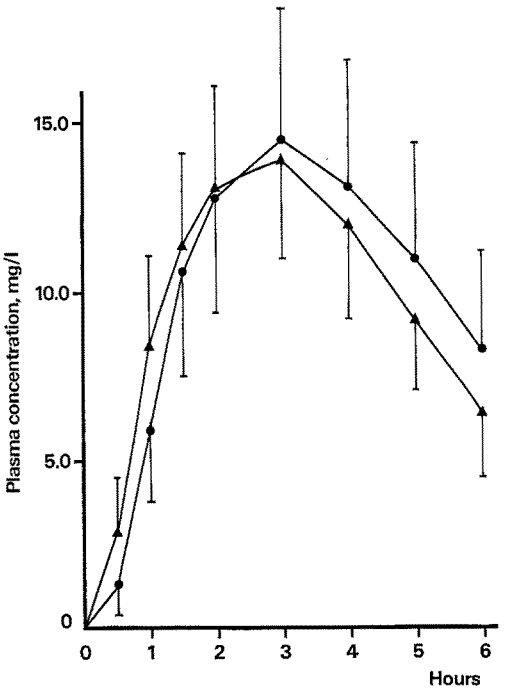


Fig. 4. Mean plasma concentration (n = 10) of tranexamic acid after a single oral dose of 2 g. ▲ = fasting conditions. ● = with a meal. Bars indicate + or – one SD

ples were taken beyond 12 h, the values of γ obtained from urinary excretion rate data are the better estimates.

Oral Study

The results of the plasma and urine sample analyses are given in Table 5. The mean plasma concentration curves are given in Fig. 4.

The mean maximum plasma concentration of tranexamic acid of 14.4 ± 3.0 (SD) mg/l when the dose was given under fasting conditions was not significantly different from the mean plasma concentration of 14.8 ± 3.7 (SD) mg/l when tranexamic acid was administered with food. Nor was there a significant difference between treatment for the mean time to reach maximum concentration (2.8 ± 0.7 and 2.9 ± 0.7 h respectively), the AUC from zero to six hours (59.5 ± 11.1 and 61.3 ± 15.0 $mg \cdot l^{-1} \cdot h^{-1}$ respectively) and the mean 24 h urinary excretion (639 ± 127 and 669 ± 154 mg respectively) of tranexamic acid.

The systemic bioavailability of tranexamic acid, calculated by comparing 0–24 h urinary excretion after oral and intravenous administration, was 33.4%

(fasting) and 34.9% (with food). The 0–24 h urinary excretion per gram of tranexamic acid after intravenous administration was 955, 972 and 950 mg for subjects L. L., O. E. and SN, respectively, mean 959 mg/g. The missing fraction for subject SN was interpolated from the urinary excretion rate versus time curve. Comparison of the infinite AUC after oral and intravenous administration gave a systemic bioavailability of 27 and 29%, respectively. These values are probably too low, depending on the method of determining the oral AUC.

The mean renal clearance of tranexamic acid was 137 ml/min when the dose was taken on an empty stomach, and 131 ml/min when the tablets were administered with food.

Discussion

In a previous paper (Eriksson et al. 1974) the pharmacokinetics of tranexamic acid after intravenous administration to healthy volunteers was reported. The analytical procedure employed made it possible to follow the plasma concentrations of tranexamic acid for eight hours after an intravenous dose. The plasma concentration versus time curve could be described by a bi-exponential equation. The development of a gas chromatographic procedure (Vessman and Strömberg 1977) permitted us to follow the plasma concentrations of tranexamic acid for 32 h after an intravenous dose of one gram. This study has shown that in order to describe the plasma concentration-time curve accurately, a three term exponential equation is required. A slow monoexponential third phase is consistent with urinary excretion of tranexamic acid continuing over a period of three days after a single intravenous dose.

The combined results from in vitro experiments (Andersson et al. 1968) and from clinical trials (Nilsson and Rybo 1967; Hedlund 1969; Tovi et al. 1972; Tovi 1973; Cormack et al. 1973) suggest that a plasma concentration of tranexamic acid of 5–10 mg/l is sufficient to inhibit fibrinolysis to a therapeutically effective degree. In the intravenous study, a level of 5 mg/l was reached approximately six hours after the dose. After a single 2 g oral dose, the blood level after six hours was also in the range of 5–10 mg/l.

The AUC from time zero to infinity, $A/\alpha + B/\beta + C/\gamma$, also represents the amount that has been eliminated from the body. By comparing the magnitudes of A/α, B/β and C/γ it is seen that $A/\alpha + B/\beta$ accounts for 88%, 66% and 74% of the total AUC for subjects L. L., O. E. and SN, respectively. This means that the major part of the elimination takes place during the 'α-phase' and the 'β-phase',

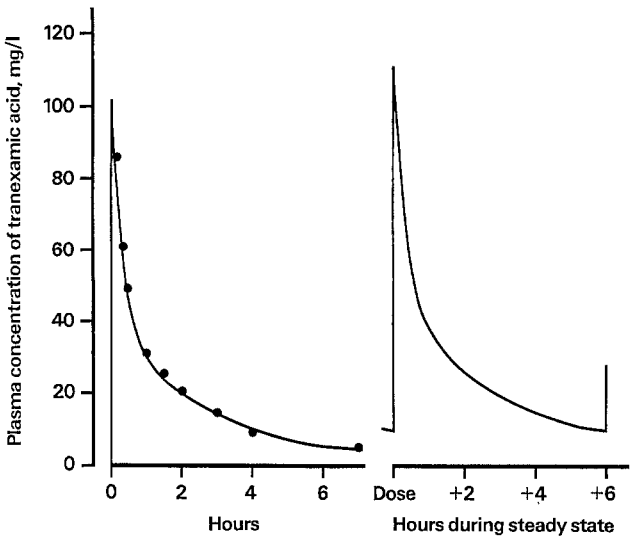


Fig. 5. Plasma concentrations of tranexamic acid after 1 g i. v. in subject L. L., and calculated plasma concentration versus time curve during steady state with 1 g doses given every 6 h. ● = experimental data. The solid curves are calculated from Eqs. 6 and 1 and, during steady state, according to Westlake (1971)

i. e. during the first 6–8 h after the dose. If a dose of tranexamic acid 1 g is given every 6 h, the 'steady state' concentration in plasma is determined chiefly by A, B, α and β, and is only influenced by C and γ to a minor degree. For practical purposes, the elimination half-life of tranexamic acid, therefore, can be set equal to $0.693/\beta$, i. e. approximately 2 h. During steady state (1 g i. v. every 6 h) the maximum plasma concentration can be calculated (Westlake 1971) to be 111, 110 and 109 mg/l for subjects L. L., O. E. and SN respectively. The calculated minimum steady state concentrations are 9.5, 10.2 and 10.4 mg/l, respectively (Fig. 5).

Calculation of the overall plasma clearance (almost equal to overall renal clearance) was done without correction for protein binding. Tranexamic acid is bound to plasma proteins, but only to a limited extent at therapeutic levels. The component in plasma mainly responsible for the binding is plasminogen (Widlund et al. 1979). The binding capacity was small and was not significantly different from zero at plasma concentrations of tranexamic acid exceeding 5 mg/l (Widlund et al. 1979). Thus, in the calculation of plasma clearance at therapeutic levels of tranexamic acid, there is no need to correct for protein binding.

Calculation of the systemic bioavailability of tranexamic acid after oral administration (about 34%), is based on comparison of 0–24 h urinary excretion data. Although the urinary excretion of tranexamic acid was not complete 24 h after

administration, the comparison gives a good estimate of bioavailability. The use of mean values from two groups of subjects is a further source of error. However, since the renal clearance did not differ significantly between the two groups, the calculations are reasonably accurate. The renal clearance of 131 and 137 ml/min after oral administration is probably an overestimate of the true value, due to the method of calculating the residual AUC.

In a study using orally administered ^{14}C-labelled tranexamic acid, Widlund et al. (1979) found a urinary recovery of radioactivity of 53% of the dose in two healthy volunteers, with no difference between 0.5 and 2 g doses. Assuming a total metabolism of less than 10%, a bioavailability of about 43% was estimated. This is within the range of the present study.

The absence of an effect of food on maximum plasma concentration, time to reach the maximum concentration, 0–24 h urinary excretion and AUC from zero to six hours after oral administration shows that food does not interfere with the absorption of tranexamic acid. This is a definite advantage in practical therapeutics.

References

1. Andersson L, Nilsson IM, Colleen S, Granstrand B, Melander B (1968) Role of urokinase and tissue activator in sustaining bleeding and the management thereof with EACA and AMCA. Ann NY Acad Sci 146: 642–656
2. Boxenbaum HG, Riegelman S, Elashoff RM (1974) Statistical estimations in pharmacokinetics. J Pharmacokinet Biopharm 2: 123–148
3. Cormack F, Chakrabarti RR, Jouhar AJ, Fearnley GR (1973) Tranexamic acid in upper gastrointestinal haemmorhage. Lancet 1: 1207–1208
4. Eriksson O, Kjellman H, Pilbrant Å, Schannong M (1974) Pharmacokinetics of tranexamic acid after intravenous administration to normal volunteers. Eur J Clin Pharmacol 7: 375–380
5. Hedlund PO (1969) Antifibrinolytic therapy with cyklokapron in connection with prostatectomy. A double blind study. Scand J Urol Nephrol 3: 177–182
6. Metzler CM, Elfring GL, McEwen AJ (1974) A users manual for NONLIN and associated programs. Research Biostatics. Upjohn Co, Kalamazoo, MI
7. Niazi S (1976) Errors involved in instantaneous intravascular input assumption. J Pharm Sci 65: 750–752
8. Nilsson L, Rybo G (1967) Treatment of menorrhagia with an antifibrinolytic agent, tranexamic acid (AMCA). A double blind investigation. Acta Obstet Gynecol Scand 46: 572–580
9. Tovi D, Nilsson IM, Thulin C-A (1972) Fibrinolysis and subarachnoid haemmorhage. Inhibitory effect of tranexamic acid. A clinical study. Acta Neurol Scand 48: 393–402
10. Tovi D (1973) The use of antifibrinolytic drugs to prevent early recurrent aneurysmal subarachnoid hemmorhage. Acta Neurol Scand 49: 163–175
11. Vessman J, Strömberg S (1977) Determination of tranexamic acid in biological material by electron capture gas chromatography after direct derivatization in an aqueous medium. Anal Chem 49: 369–373
12. Wagner JG and coworkers (1977) Pharmacokinetic parameters estimated from intravenous data by uniform methods and some of their uses. J Pharmacokinet Biopharm 5: 161–183
13. Westlake W (1971) Problems associated with analysis of pharmacokinetic models. J Pharm Sci 60: 882–885
14. Widlund L, Strömberg S, Hallström H, Osanius B (1979) The disposition of tranexamic acid (AMCA) in different animal species and in man after oral dosage. Scientific Report No. 7999047, Kabi AB, Stockholm

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