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Special Considerations with Regard to the Dosage of Tranexamic Acid in Patients with Chronic Renal Diseases

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Summary. Tranexamic acid is a potent antifibrinolytic drug frequently used in the treatment of haematuria and a number of other haemorrhagic conditions. Since it is eliminated mainly in the urine, the drug accumulates in patients with uraemia. The excretion of tranexamic acid in patients with renal failure has been investigated and dosage recommendations are given for tranexamic acid therapy in cases of renal failure.

Key words: Tranexamic acid - Pharmacokinetics - Uraemia - Impaired renal function.

Tranexamic acid is an antifibrinolytic drug that reduces bleeding either induced or sustained by local fibrinolytic acitivity in the tissues and body fluids. Examples include bleeding from the urinary tract (2, 6, 11), menorrhagia, recurrent bleeding after cone biopsy of the cervix (8, 10, 13), subarachnoid haemorrhages (12) and traumatic hyphaema (4, 7). Occasionally it may be due to pathologically raised fibrinolytic activity. Rybo (9) has shown that in many women suffering from menorrhagia the plasminogen activator activity in the endometrium is raised at the time of menstruation. However, in these patients it is not a case of abnormally raised fibrinolytic activity, but that the plasminogen activators normally present dissolve haemostatic clots in the damaged tissue. Tranexamic acid inhibits the activation of plasminogen induced by activators in the tissues and body fluids. This is the mechanism of the haemostatic effect.

Intravenous tranexamic acid is eliminated entirely via the kidneys (1, 5). In patients with impaired renal function it is important to adjust the dosage to their ability to excrete the drug so as to avoid the risk of accumulation with increasing plasma concentrations (3). The purpose of the present study was to investigate the plasma concentration and the amount of tranexamic acid excreted in the urine after a single intravenous injection of tranexamic acid in patients with impaired renal function.

MATERIAL AND METHODS

Twenty-eight patients with chronic renal disease: glomerulonephritis, pyelonephritis, nephrosclerosis or longstanding urinary obstruction, and all with reduced renal function, were divided into four groups with respect to the degree of functional impairment. Group I (n = 6) had serum creatinine concentrations of 120-249 μmol/l, Group II (n = 7) 250-500 μmol/l and Groups III (n = 6) and IV (n = 9) > 500 μmol/l.

Tranexamic acid (Cyklokapron, solution for injection 0.1 g/ml, AB Kabi, Stockholm) was administered intravenously in a dose of

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Table 1. Group I. The concentration of tranexamic acid in plasma (mg/l) after an i.v. injection of 10 mg per kg body weight to patients with serum creatinine concentrations of 120 to 249 µmol/l

Serum creatinine (µmol/l)	Patient (initials)	Hours after the injection						
		0.0	0.5	1.0	3.0	5.0	8.0	24.0
133	E.J.	0.6	32.3	26.0	13.5	9.1	5.5	1.3
186	K.A.S.	0.2	28.8	23.3	12.0	11.8	n.d.	2.3
186	G.S.	0.2	28.8	23.3	12.0	11.8	n.d.	2.3
186	K.W.	1.8	35.5	29.5	18.5	15.5	5.5	3.5
230	A.G.	<0.2	34.3	28.3	16.7	14.0	6.2	1.2
239	A.J.	<0.4	34.0	28.3	19.3	16.5	11.8	3.5
Mean			32.3	26.5	15.3	13.1	7.3	2.4
S.D.			2.9	2.7	3.3	2.7	3.1	1.0

Table 2. Group II. The concentration of tranexamic acid in plasma (mg/l) after an i.v. injection of 10 mg per kg body weight to patients with serum creatinine concentrations of 250 to 500 µmol/l

Serum creatinine (µmol/l)	Patient (initials)	Hours after the injection						
		0.0	0.5	1.0	3.0	5.0	8.0	24.0
274	A.S.		31.3	29.0	22.2	14.6	9.5	2.3
283	J.E.		n.d.	29.0	27.0	22.0	9.5	6.0
301	I.K.	<0.4	34.3	26.3	19.7	13.2	9.4	4.3
309	S.L.	2.5	46.0	28.5	28.5	23.0	17.0	0.4
362	A.S.	1.5	39.5	27.0	21.5	17.5	15.0	5.8
389	E.N.	0.6	n.d.	21.3	16.3	16.3	15.3	5.7
460	G.A.	0.4	31.3	25.7	23.8	19.2	15.8	9.0
Mean			36.4	26.7	22.7	18.0	13.1	4.8
S.D.			6.3	2.7	4.2	3.7	3.4	2.8

10 mg per kg body weight to 19 patients in Groups I-III and in a dose of 500 mg, irrespective of body weight, to the nine patients comprising Group IV. In patients belonging to Groups I-III, blood samples were collected immediately before the injection and 1/2, 1, 3, 5, 8 and 24 h after the injection. In patients belonging to Group IV, further blood samples were collected 12, 36 and 48 h after the injection. Plasma was separated by centrifugation and stored at -20° C until assayed.

Urine was collected in fractions over a period of 24 h in Groups I-III and for 48 h in Group IV. The patients emptied their bladders immediately before the administration of tranexamic acid and at the end of each collection period. The specimens at time zero were kept as controls and samples were obtained for the

Table 3. Group III. The concentration of tranexamic acid in plasma (mg/l) after an i.v. injection of 10 mg per kg body weight to patients with serum creatinine concentrations of >500 µmol/l

Serum creatinine (µmol/l)	Patient (initials)	Hours after the injection						
		0.0	0.5	1.0	3.0	5.0	8.0	24.0
504	H. A.	0.8	27.0	26.0	22.0	14.9	13.5	7.9
654	M. M.	2.3	30.7	27.0	22.3	18.6	15.7	10.8
681	J. O.	1.3	38.3	34.7	28.5	26.3	20.9	9.6
804	E. S.	0.9	33.7	30.3	24.7	21.9	14.8	8.3
813	Ö. S.	0.0	26.8	17.2	21.3	21.3	14.5	10.0
884	J. H.	0.8	n. d.	26.0	22.3	21.0	17.0	12.2
Mean			31.3	26.9	23.5	20.7	16.1	9.8
S. D.			4.8	5.8	2.7	3.8	2.6	1.6

Table 4. Group IV. The concentration of tranexamic acid in plasma (mg/l) after an i.v. injection of 500 mg tranexamic acid to patients with serum creatinine concentrations of >500 µmol/l

Serum creatinine (µmol/l)	Patient (initials)	Body weight (kg)	Hours after the injection								
			0.0	0.5	1.0	3.0	5.0	8.0	12.0	24.0	36.0	48.0
530	S. Å.	84	0.9	29.3	17.5	14.0	12.2	9.3	7.5	4.2	2.9	1.9
636	S. Ö.	41	1.1	27.1	26.3	21.5	19.2	16.3	15.7	11.7	9.6	6.8
654	C. N.	56	0.7	30.7	21.3	12.2	14.2	11.4	9.1	8.2	4.8	3.4
681	N. L.	75	0.0	63.3	10.3	n. d.	10.7	8.8	n. d.	5.8	4.8	4.2
751	K. A. J.	97	0.6	12.0	11.3	9.7	9.3	8.7	7.8	5.6	4.2	3.4
1043	B. O.	67	0.0	21.3	17.0	18.0	15.3	n. d.	14.6	7.8	6.6	4.2
1060	A. S.	77	0.0	18.5	17.0	16.3	15.3	11.5	12.1	5.4	8.6	6.3
1379	J. E.	63	0.4	31.3	8.3	9.3	7.8	6.2	5.6	5.4	5.6	5.1
1520	F. G.	71	< 1.0	86.7	16.0	15.5	13.8	11.4	11.0	8.0	6.8	5.6

periods 0-1, 1-8 and 8-24 h or 0-1, 1-8, 8-12, 12-24 and 24-48 h.

The volume of urine voided on each occasion was measured and an aliquot was stored at -20° C for subsequent analysis. Tranexamic acid was determined in the plasma and in the urine by the method described by Eriksson et al. (5).

RESULTS

Group I

The results of plasma concentration and urinary excretion studies are shown in Tables 1 and 6. The plasma concentrations 8 and 24 h after injection averaged 7.3 ± 3.1 and

Table 5. Groups I-III. The mean value of the concentration of tranexamic acid (mg/l) in plasma after an i.v. injection of 10 mg per kg body weight to patients with various degrees of renal insufficiency

Serum creatinine (μmol/l)	Hours after the injection					
	0.5	1.0	3.0	5.0	8.0	24.0
120 to 249	32.3	26.5	15.3	13.1	7.3	2.4
250 to 500	36.4	26.7	22.7	18.0	13.1	4.8
>500	31.3	26.9	23.5	20.7	16.1	9.8

2.4 ± 1.0 mg/l respectively. For technical reasons, the amount of tranexamic acid excreted in 24 hours could be determined in only two patients (A. J. and A. G.), the figures being 50.6 % and 54.6 % respectively.

Group II

The plasma concentration and urinary excretion findings are presented in Tables 2 and 6. The plasma concentrations 8 and 24 h after injection averaged 13.1 ± 3.4 and 4.8 ± 2.8 mg/l. On the average, 38.6 ± 13.1 % of the administered dose was excreted in 24 h.

Group III

The results of the plasma concentration and urinary excretion investigations are shown in Tables 3 and 6. The plasma concentrations 8 and 24 h after injection averaged 16.1 ± 2.6 mg/l and 9.8 ± 1.6 mg/l respectively. On an average, 19.2 ± 5.5 % of the administered dose was excreted in 24 h.

A summary of the findings in groups I-III is given in Table 5.

Group IV

The plasma concentration and urinary excretion findings for patients receiving a dose of 500 mg tranexamic acid irrespective of body weight and followed up for 48 h are presented in Tables 4 and 6. During the first 24-h period 3.1-36.7 % of the administered dose was excreted, while 6.0-51.2 % was excreted over 48 h.

DISCUSSION

The biological half-life of tranexamic acid after intravenous administration has been reported to be 1.9 and 2.7 hours in two healthy subjects (5). Eight hours after the administration of a single intravenous injection of 1 g the concentration of tranexamic acid in the plasma was 2.0 mg/l and 2.8 mg/l. Calculated from the curve, the plasma concentration at 24 hours was only about 0.5 mg/l. Andersson et al. (1) administered 10 mg tranexamic acid per kg body weight intravenously to 10 male volunteers. In that study the serum concentrations 1, 3 and 5 hours after the administration averaged 18.3, 9.6 and about 5 mg/l. As shown in Table 5, the serum concentrations five hours after administration of the same dose in three different groups of patients with impaired renal function were 13.1, 18.0 and 20.7 mg/l. In contrast with the findings in individuals with normal renal function, tranexamic acid could still be demonstrated in the plasma of the patients 24 hours after the injection. The highest concentrations occurred in the group with the highest creatinine values. In the patients who were followed for 48 hours after an injection of 500 mg tranexamic acid, the concentration was 1.9-6.8 mg/l. A plasma concentration of about 5-10 mg/l is sufficient to inhibit fibrinolysis.

The biological half-life calculated for some of the patients in Group IV ranged from 18 to 38 hours, which is considerably longer than that for patients with normal renal function. Even with moderate azotaemia the half-life is considerably longer than that found in individuals with normal renal function (5).

In five normal volunteers the mean total recovery from the urine has been found to be 92.3 % and 94.8 % of the intravenously administered dose at 24 and 48 hours respectively (5). This agrees with the findings published by Andersson et al. (1). In patient Groups II and III 24-hour recovery of 40.9 and 20.3 % respectively were noted. In Group IV the 48-hour recovery ranged from 6.0 to 51.2 %. In the two patients with the

Table 6. Per cent of the dose of tranexamic acid excreted following intravenous injection in patients with different serum creatinine values

Group No.	Serum creatinine (μmol/l)	Patient (initials)	Per cent of dose excreted 0 - 24 h	0 - 48 h
I	133	EJ	n. d.	n. d.
	186	GS	n. d.	n. d.
	186	KW	n. d.	n. d.
	230	AG	54.6	n. d.
	239	AJ	50.6	n. d.
II	274	AS	57.6	n. d.
	283	JE	44.1	n. d.
	301	IK	34.4	n. d.
	309	SL	32.3	n. d.
	362	AS	52.4	n. d.
	389	EN	23.1	n. d.
	460	GA	26.6	n. d.
Average			38.6 ± 13.1	
III	504	HA	19.9	n. d.
	654	MM	10.9	n. d.
	681	JO	24.4	n. d.
	804	ES	16.8	n. d.
	813	ÖS	25.8	n. d.
	884	JH	17.5	n. d.
Average			19.2 ± 5.5	
IV	530	SÅ	36.7	51.2
	636	SÖ	33.0	37.1
	681	NL	24.4	37.7
	751	KAJ	30.9	49.3
	840	ÅL	19.8	29.0
	1043	BO	20.6	30.9
	1060	AS	12.3	n. d.
	1379	JE	5.1	10.1
	1520	FG	3.1	6.0
Average			20.7 ± 20.0	31.4 ± 14.9

highest creatinine values, viz. 1389 and 1520 µmol/l, the quantities excreted amounted to only 10.1% and 6.0% respectively.

In haemorrhagic conditions in which treatment with tranexamic acid is indicated to inhibit local finbrinolytic activity, impaired renal function does not constitute a contraindication. However, in order to avoid accumulation of the drug, it should be given at longer intervals than for patients with normal renal function. Whereas in normal cases use can be made of a standardised dosage scheme for tranexamic acid, generally 1 g two to four times daily, when renal function is reduced the dosage should be adjusted to the patient's weight, and the preparation should be given at longer intervals.

The following dosage scheme can be recommended: In patients with serum creatinine concentrations of 120 to 250 µmol/l, 10 mg tranexamic acid per kg body weight i. v. twice daily. At serum creatinine levels of 250 to 500 µmol/l the dosage should be 10 mg per kg body weight i. v. at 24-hourly intervals, and at serum creatinine levels of 500 µmol/l or more the same dose should be given with an interval of 48 hours between doses.

It should be pointed out that tranexamic acid therapy is not indicated in haematuria caused by diseases of the renal parenchyma. Intravascular precipitation of fibrin frequently occurs in these conditions and may aggravate the disease. In addition, in cases of massive renal haemorrhage of any cause, antifibrinolytic therapy carries the risk of clot retention in the renal pelvis.

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