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The Acute Effects of FK-506 on Renal Haemodynamics, Water and Sodium Excretion and Plasma Levels of Angiotensin II, Aldosterone, Atrial Natriuretic Peptide and Vasopressin in Pigs

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Abstract

FK-506 has been shown to be an effective immunosuppressive drug with possible nephrotoxic side effects. In this study we have investigated the acute effects of FK-506 on renal haemodynamics, water, sodium and lithium excretion rates and plasma levels of angiotensin II, aldosterone, atrial natriuretic peptide (ANP) and vasopressin in 29 anaesthetized Lancaster/Yorkshire female pigs. A continuous intravenous infusion was given over a 2-h period to 4 groups: A: 0·075 mg kg^{-1} (n = 7), B: 0·15 mg kg^{-1} (n = 8), C: 0·3 mg kg^{-1} (n = 6) and P: placebo vehicle (n = 8). Glomerular filtration rate (GFR) and renal plasma flow (RPF) were measured by the constant infusion clearance technique using 125-I-iothalamate and 131-I-hippuran as reference substances. Hormonal parameters were measured by radioimmunoassay.

In all three FK-506 groups, fractional lithium excretion was significantly decreased 2 h after FK506 infusion (P: +0·4%, A: −8·8% ($P < 0.05$), B: −12·9% and C: −11·2% ($P < 0.01$ for both). Mean arterial blood pressure (MBP) was significantly increased in the two highest dosage groups (B,C) at 2 h of infusion: (MBP; P: +2·9%, A: +3·5%, B: +12·0%, C: +15·3% ($P < 0.01$ for both). GFR and RPF showed minor and inconsistent changes while all other parameters measured showed similar or no changes.

In conclusion, acute infusion of FK-506 to pigs does not change overall renal function significantly, but increases mean arterial blood pressure and decreases fractional excretion of lithium.

FK-506 is a new macrolide immunosuppressive agent isolated from the fungus *Streptomyces tsukubaensis* and has recently been shown to possess almost similar immunsuppressive potentials to cyclosporin A (Lautenschlager et al 1991; Klintmalm 1994; The US Multicenter FK-506 Liver Study Group 1994), probably because the two drugs have almost similar effects on the immune system (Sawada et al 1987; Zeevi et al 1987). FK-506 is however, approximately 100 times more potent than cyclosporin A. The nephrotoxic side-effect of cyclosporin A and the development of hypertension observed during cyclosporin A treatment also seem to be characteristic side effects of FK-506.

The mechanism behind the nephrotoxic side-effect of FK-506 has been suggested to involve a reduction in both glomerular filtration rate and in renal plasma flow; however, studies in larger animals and humans are necessary to fully clarify both the acute and chronic effects of FK-506 on renal haemodynamics, tubular function, vasoactive hormones and the systemic blood pressure.

Since no thorough investigation of the acute effects of FK-506 on renal haemodynamics, renal sodium and water handling and hormonal parameters with importance for renal sodium and water handling have been performed in larger animals or in humans, we have investigated the acute effects of intravenous infusion of FK-506 on glomerular filtration rate, renal plasma flow, renal excretion rates of sodium, water and lithium and plasma levels of angiotensin II, aldosterone, atrial natriuretic peptide, vasopressin, and mean arterial blood pressure and heart rate in anaesthetized non-transplanted pigs in a placebo-controlled dose-response study.

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Materials and Methods

Animals

Immature (90-day-old) female pigs of the Lancaster/Yorkshire breed, mean body weight 33 kg (range 30–36), were fed a normal diet and had free access to water. From the day before the experiments, the animals were deprived of food, but still had free access to water up to one hour before the study.

Drugs

FK-506 (Fujisawa, Japan) was provided as a white powder and was dissolved in ethanol : Tween (3 : 1, v/v) then further diluted with saline. The placebo vehicle was prepared in the same manner except for FK-506.

Animal preparation

Pigs were randomized into one of four groups. Group A, receiving a total FK-506 dose of 0·075 mg kg^{-1} (n = 7); group B: 0·15 mg kg^{-1} (n = 8); group C: 0·3 mg kg^{-1} (n = 6) and group *P* receiving the placebo vehicle (n = 8). At 2000 h the evening before the study each pig was given 300 mg lithium carbonate orally. Sedation before transportation to the hospital was obtained by an intramuscular injection of a mixture of azaperonum (Sedoparone 4 mg kg^{-1}) and midazolam (Dormicum 0·5 mg kg^{-1}). After arrival at the operating room, the pigs were initially anaesthetized with an intravenous injection of metomidate hydrochloride (Hypnodil

2 mg kg^{-1}) and subsequently intubated and coupled to a volume-controlled respirator (Servo 900 D, Siemens-Elema Sweden) ventilated with a gas mixture of O_2 and N_2O (6:1) using halocarbon (halothane 0·5–1%) for maintaining anaesthesia. Tidal volume and rate of respiration were adjusted according to arterial gas analysis every hour throughout the study (7.35 < pH < 7.45). The pigs were placed on a heating blanket, and body temperature was continuously monitored, (by a rectally placed digital thermometer) and kept between 36·5 and 37·5°C. A catheter (Venflon 1.2 mm) was placed in a subcutaneous vein in each ear for infusion of ^{125}I-iothalamate, ^{131}I-hippurane, FK-506 and isotonic saline (0·2 mL min^{-1} kg^{-1}). A catheter (Fast-Cath 7·0 Fr) was guided through the femoral vein up into the inferior vena cava for blood sampling; another catheter (6·0 Fr) was guided through the femoral artery up into arteria iliaca communis for measurements of blood pressure and heart rate, via a transducer (Medex inc.) connected to a Kone Patient Data Monitor 565 A (Kone Corp. Instrument Division, Finland). A catheter was placed in the bladder by cystoscopy.

Sampling procedure

After an equilibration period of 120 min urine was collected for determination of glomerular filtration rate (GFR), renal plasma flow (RPF), lithium clearance (C_{Li}), fractional lithium excretion (FE_{Li}) and sodium and water excretion rates, in nine clearance periods of 30 min each. After the first control clearance period FK-506 or placebo was given intravenously during the next four clearance periods. FK-506 was given at a dose of 0·075 mg kg^{-1} (group A), 0·15 mg kg^{-1} (group B) and 0·30 mg kg^{-1} (group C). At the beginning and the end of each clearance period blood samples were drawn for determination of serum values of ^{125}I-iothalamate, ^{131}I-hippuran, lithium and sodium. Blood samples for determination of the plasma concentration of angiotensin II, aldosterone, atrial natriuretic peptide (ANP) and vasopressin were drawn before FK 506 administration, and at 60 and 120 min during FK 506 infusion and a further 60 and 120 min after FK-506 infusion cessation. Blood pressure and heart rate were measured at the end of each clearance period. The pigs was anaesthetized during the whole study and at the end of the study the kidneys were taken out and weighed, the pigs were then killed with an overdose of intravenous potassium.

Methods

GFR and RPF were measured by the constant infusion clearance technique using ^{125}I-iothalamate and ^{131}I-hippuran as reference substances. A priming dose ensured a serum activity of 800–1600 counts min^{-1} mL^{-1} for ^{125}I-iothalamate and 200–600 counts min^{-1} mL^{-1} for ^{131}I-hippuran. Serum activity was kept stable by constant intravenous infusion with an Terufusion syringe pump (model STC-521, Terumo, Tokyo, Japan).

All clearance calculations are based on the formula:

$$\text{clearance of a substance X is } CX = Cu * V/Cp \quad (1)$$

where C_u is the concentration in urine, V the urinary output and C_p the mean value of the two plasma values before and after each clearance period.

Angiotensin II in plasma was measured by radioimmunoassay by a modification of the method described by Kappelgaard et al (1976). Radioimmunoassay was performed after previous extraction from plasma by Sep-Pak C_{18} cartridges (Water Associates, MA, USA). The antibody was obtained from Department of Clinical Physiology, Glostrup Hospital, Denmark. The minimal detection level was 2 pmol L^{-1} plasma. The coefficients of variation were 12% (interassay) and 8% (intra-assay).

Aldosterone in plasma was measured by a slight modification of a previously described method (Rask-Madsen et al 1974). Using a rabbit-antialdosterone antibody (International CIS, France) radioimmunoassay was performed on a residue from plasma prepared by extraction with dichloromethane and purification on silica gel columns. The minimum detection level was 42 pmol L^{-1}. The coefficients of variation were 13% (interassay) and 9% (intra-assay).

ANP in plasma was determined by radioimmunoassay as previously described (Thomassen et al 1987). ANP was extracted from plasma by means of Sep-Pak C_{18} cartridges. For radioimmunoassay rabbit-anti-ANP antibody was obtained from Department of Clinical Chemistry, Bispebjerg Hospital, Copenhagen, Denmark. The minimum detection level was 0·5 pmol L^{-1} plasma. The coefficients of variation were 12% (interassay) and 10% (intra-assay).

Vasopressin was measured radioimmunologically by a slight modification of the method previously described (Pedersen et al 1984). Before the assay procedure, plasma proteins were precipitated with cold acetone, and lipids extracted with petroleum ether. Radioimmunoassay was performed using a rabbit-antivasopressin antibody (ICM Immuno-Chemicals, Tuma, Sweden). The minimum detection level was 0·5 pmol L^{-1}. The coefficients of variation were 13% (interassay) and 9% (intra-assay). Serum and urinary concentrations of lithium were measured by atomic absorption spectrophometry. Plasma and urinary concentrations of sodium were measured by routine methods at the Department of Clinical Chemistry, Skejby Hospital.

Statistical analysis

The values are presented as five time periods. Before (−30–0 min) which is the values obtained during basal conditions. The rest are presented as the mean value of two clearance periods: during infusion: (0–60 min), (60–120 min) and after infusion cessation: (120–180 min) and (180–240 min). Non-parametric tests were used for the statistical analyses. A distribution-free test for multiple comparisons based on Friedman's rank sum test was used for multiple paired comparison within the group. Dunn's test for multiple comparisons based on Kruskal-Wallis rank sums were used for unpaired comparisons between groups. A P value of 0.05 was considered as the limit of significance.

Results

Mean blood pressure and heart rate

Mean blood pressure (MBP) and heart rate (HR) are given in Table 1. During basal conditions there were no significant differences in MBP and HR between the groups. During the second hour of infusion MBP increased significantly in the two highest dosage groups (P: +2·9%, A: +3·5%, B: +12·0% and C: +15·3%, $P < 0.01$) and continued to be significantly higher

Table 1. Mean blood pressure (MBP) and heart rate (HR) determined after each of nine consecutive clearance periods, before, during and after an intravenous infusion of FK-506. The values during and after infusion are means of two clearance periods each of 30 min duration.

	Before	During infusion		After infusion	
	− 30–0	0–60	60–120	120–180	180–240
MBP (mmHg)					
Placebo	70	70	71	73	70
(n = 8)	(63-75)	(65–75)	(65–75)	(62–76)	(60–71)
0.075 mg kg^{-1}	70	71	69	66	64
(n = 7)	(53–72)	(54–77)	(55–78)	(53–73)	(52–71)
0.150 mg kg^{-1}	70	68	73**	76**	69
(n = 8)	(61–79)	(65–83)	(69–88)	(69–85)	(65–86)
0.300 mg kg^{-1}	65	68	76**	75**	73**
(n = 6)	(59–75)	(60–79)	(71–81)	(64–80)	(61–81)
HR (beats min^{-1})					
Placebo	68	68	66	64	65
(n = 8)	(60-70)	(60–72)	(61–71)	(61–69)	(62–67)
0.075 mg km^{-1}	68	68	72	72	72
(n = 7)	(68–72)	(64–72)	(62–76)	(60–76)	(62–76)
0.150 mg kg^{-1}	76	75	75	75	76
(n = 8)	(75–81)	(73–82)	(72–85)	(73–84)	(72–83)
0.300 mg kg^{-1}	74	71	71	70	70
(n = 6)	(64–76)	(64–74)	(62–76)	(66–76)	(64–76)

Medians with 1st and 3rd quartile in parentheses. *$P \leq 0.05$ and ** $P \leq 0.01$ within groups.

after cessation of the infussion. HR was not significantly changed.

GFR, RPF and filtration fraction

GFR and RPF are given in Table 2. At basal conditions no significant differences were found between the four groups in any of the three parameters. GFR increased slightly during the second hour of FK-506 infusion in the two highest dosage groups (B and C) which resulted in significant differences between the value in the placebo group and the values in group B and C in that period (60–120 min). GFR tended to increase throughout the study periods in the placebo group. This resulted in a significant difference between basal GFR and GFR measured 2 h after infusion cessation. Otherwise no significant changes were observed in the other groups or in RPF and FF. There were no significant differences in the percentage change in the parameters between any of the groups.

Urinary output, urinary sodium excretion, fractional sodium excretion, lithium clearance and fractional lithium excretion

Urinary output (V), urinary sodium excretion (U_{Na}) and fractional sodium excretion (FE_{Na}) are given in Table 3 and lithium clearance (C_{Li}) and fractional lithium excretion (FE_{Li}) are given in Table 4. There was no significant difference between the groups before and during infusion for all five parameters. Two hours after FK-506 infusion cessation FE_{Li} had decreased significantly in all three FK-506 infusion groups (P: 0.4%, A: −8.8%, B: −12.9% and C: −11.2%, $P < 0.05$). No significant changes were observed in the other parameters.

Table 2. Glomerular filtration rate (GFR) and renal plasma flow (RPF) determined in nine consecutive clearance periods (min), before, during and after an intravenous infusion of FK-506, 0.075 mg kg^{-1}. The values during and after infusion are means of two clearance periods each of 30-min duration.

	Before	During infusion		After infusion	
	− 30–0	0–60	60–120	120–180	180–240
GFR (mL min^{-1})					
Placebo	62	67	69	70	71*
(n = 8)	(56–68)	(61–78)	(64–80)	(64–79)	(63–82)
0.075 mg kg^{-1}	73	77	71	76	68
(n = 7)	(50–81)	(64–81)	(55–92)	(53–84)	(49–87)
0.150 mg kg^{-1}	67	67	73**	69	70
(n = 8)	(47–76)	(58–83)	(66–85)	(59–82)	(57–83)
0.300 mg kg^{-1}	71	74	82**	82	80
(n = 6)	(67–83)	(71–79)	(75–94)	(75–86)	(77–81)
RPF (mL min^{-1})					
Placebo	167	174	181	192	190
(n = 8)	(155–188)	(158–216)	(173–226)	(164–222)	(156–235)
0.075 mg kg^{-1}	208	200	196	206	201
(n = 7)	(140–216)	(185–219)	(173–270)	(50–224)	(143–250)
0.150 mg kg^{-1}	182	180	202	170	162
(n = 8)	(119–211)	(136–234)	(158–225)	(149–224)	(140–231)
0.300 mg kg^{-1}	196	200	242	227	214
(n = 6)	(182–228)	(189–207)	(212–255)	(199–266)	(207–238)

Medians with 1st and 3rd quartile in parentheses. *$P \leq 0.05$ and **$P \leq 0.01$ within groups.

Table 3. Urinary output (V), urinary sodium excretion (U_{Na}) and fractional sodium excretion (FE_{Na}) determined in nine consecutive clearance periods (min), before, during and after an intravenous infusion of FK-506. The values during and after infusion are means of two clearance periods each of 30-min duration.

	Before	During infusion		After infusion	
	−30–0	0–60	60–120	120–180	180–240
V (mL min^{-1})					
Placebo (n = 8)	5.2 (4.2–8.2)	5.7 (4.8–6.1)	6.2 (5.4–7.3)	6.5 (7.0–5.2)	5.2 (4.7–6.4)
0.075 mg kg^{-1} (n = 7)	6.7 (5.6–7.9)	6.2 (5.9–8.8)	7.3 (5.5–8.3)	6.2 (4.2–7.0)	5.1 (3.3–6.6)
0.150 mg kg^{-1} (n = 8)	4.9 (2.0–8.6)	5.2 (2.2–7.4)	6.1 (5.8–9.2)	6.4 (5.0–7.7)	6.2 (6.3–7.0)
0.300 mg kg^{-1} (n = 6)	4.7 (2.0–8.6)	4.8 (2.2–7.4)	6.8 (5.8–9.2)	6.2 (5.0–7.7)	6.2 (6.3–7.0)
U_{Na} (mmol min^{-1})					
Placebo (n = 8)	708 (584–1010)	771 (702–8634)	784 (734–1035)	911 (768–1009)	782 (696–973)
0.075 mg kg^{-1} (n = 7)	917 (745–997)	840 (789–1319)	914 (838–1266)	819 (612–1101)	742 (550–977)
0.150 mg kg^{-1} (n = 8)	620 (540–837)	699 (540–767)	886 (636–1158)	865 (667–966)	736 (527–935)
0.300 mg kg^{-1} (n = 6)	640 (256–1087)	680 (267–954)	903 (788–1214)	876 (727–996)	858 (554–977)
FE_{Na} (%)					
Placebo (n = 8)	6.8 (6.5–11.6)	7.5 (6.7–8.5)	8.8 (7.4–9.3)	9.3 (7.3–9.5)	8.1 (6.9–8.8)
0.075 mg kg^{-1} (n = 7)	9.3 (6.8–12.8)	9.9 (7.2–12.5)	9.2 (8.8–12.0)	8.6 (7.4–11.5)	7.5 (5.7–9.5)
0.150 mg kg^{-1} (n = 8)	7.5 (6.1–8.5)	6.3 (5.5–7.1)	7.2 (6.2–10.2)	7.3 (6.4–10.2)	6.8 (5.7–8.2)
0.300 mg kg^{-1} (n = 6)	6.8 (2.6–8.2)	6.3 (3.0-7.6)	8.3 (6.6-8.8)	7.4 (5.8–9.0)	7.1 (4.8–8.3)

Medians with 1st and 3rd quartile in parentheses. $*P \leq 0.05$ and $**P \leq 0.01$ within groups.

Table 4. Lithium clearance (C_{Li}), and fractional lithium clearance (FE_{Li}) determined in nine consecutive clearance periods (min), before, during and after an intravenous infusion of FK-506. The values during and after infusion are means of two clearance periods each of 30 min duration.

	Before	During infusion		After infusion	
	−30–0	0–60	60–120	120–180	180–240
C_{Li} (mL min^{-1})					
Placebo (n = 8)	24.7 (22.8–27.4)	27.0 (23.3–30.7)	29.5 (26.2–34.5)	30.7 (26.9–33.4)	30.4 (23.2–35.8)
0.075 mg kg^{-1} (n = 7)	29.2 (20.2–33.7)	29.4 (22.9–31.7)	29.1 (21.0–33.9)	28.6 (18.3–32.7)	26.3 (16.4–32.0)
0.150 mg kg^{-1} (n = 8)	25.5 (21.6–27.6)	26.4 (21.9–30.5)	27.2 (23.1–31.7)	23.2 (21.3–31.2)	23.9 (19.5–29.0)
0.300 mg kg^{-1} (n = 6)	27.2 (22.3–37.0)	28.3 (18.4–32.5)	29.2 (26.0–36.1)	28.0 (24.0–33.4)	28.6 (20.1–33.0)
FE_{Li} (%)					
Placebo (n = 8)	40.3 (38.5–41.0)	38.2 (36.2–42.4)	42.1 (38.1–44.9)	41.2 (39.0–46.7)	42.0 (34.4–45.5)
0.075 mg kg^{-1} (n = 7)	41.3 (41.3–45.1)	40.8 (36.4–45.7)	41.0 (36.6–44.6)	41.0 (35.0–42.6)	38.7* (32.4–40.4)
0.150 mg kg^{-1} (n = 8)	37.3 (35.8–40.7)	36.4 (33.7–37.3)	35.8 (32.8–37.5)	34.2 (32.8–38.3)	33.8** (29.0–37.3)
0.300 mg kg^{-1} (n = 6)	38.0 (32.7–46.5)	35.1 (26.2–43.6)	36.9 (28.7–42.4)	36.8 (29.1–39.04)	34.8** (25.9–38.7)

Medians with 1st and 3rd quartile in parentheses. $*P \leq 0.05$ and $**P \leq 0.01$ within groups.

Angiotensin II, aldosterone, vasopressin and atrial natriuretic peptide

The values for plasma level of angiotensin II, aldosterone, ANP and vasopressin are given in Table 5.

During basal conditions there were no significant differences between the plasma levels of the hormones in the four groups. After cessation of FK-506 infusion angiotensin II had decreased in the placebo group and the two lowest dosage groups (A and B) while angiotensin II remained unchanged in the highest FK-506 dosage group C. Atrial natriuretic peptide

Table 5. Plasma level of angiotensin II, aldosterone, atrial natriuretic peptide (ANP) and vasopressin determined before, during and after an intravenous infusion of FK-506.

	Before	During infusion		After infusion	
	− 30–0	0–60	60– 120	120–180	180-240
Angiotensin II (pmol L^{-1})					
Placebo	9.6	8.1	6 .7	5.0*	3.6**
(n = 8)	(7.2–27.7)	(4.8–13.9)	(3.4–10.5)	(3.6–8.1)	(2.9-8.6)
0.075 mg kg^{-1}	12.4	5.7	5.7	4.8*	4.3**
(n = 7)	(6.7–71.7)	(5.7–49.7)	(4.8–28.7)	(3.8–24.4)	(3.4-19.1)
0.150 mg kg^{-1}	22.0	12.4	11.5	9.1	7.7**
(n = 8)	(9.6–31.1)	(5.7–20.6)	(5.3–14.1)	(4.1–14.1)	(3.4-10.3)
0.300 mg kg^{-1}	9.6	9.6	6.7	5.5	4.5
(n = 6)	(2.9–20.1)	(2.9–17.2)	(2.9–8.6)	(2.9–6.7)	(1.9-18.6)
Aldosterone (pmol L^{-1})					
Placebo	74	83	89	88	72
(n = 8)	(60–86)	(67–93)	(58–106)	(58–97)	(61–86)
0.075 mg kg^{-1}	67	53	56	78	67
(n = 7)	(50–69)	(39–94)	(50–78)	(53–99)	– (61-74)
0.150 mg kg^{-1}	54	72	69	79	78
(n = 8)	(47–92)	(49–81)	(64–81)	(51–104)	(46-121)
0.300 mg kg^{-1}	94	88	115	101	109
(n = 6)	(44–119)	(42–144)	(64–192)	(67–158)	(72–118)
ANP (pmol L^{-1})					
Placebo	7.6	7.3	6 .3	5.4	5.1**
(n = 8)	(6.6–10.8)	(6.3–9.0)	(5.6–8.1)	(5.0–7.6)	(4.7–7.1)
0.075 mg kg^{-1}	10.2	9.2	7.7	6.2**	5.6**
(n = 7)	(6.6–14.6)	(7.3–10.0)	(6.1–8.9)	(4.7–6.6)	(4.3–6.3)
0.150 mg kg^{-1}	10.0	9.9	9.1	9.2**	9.3**
(n = 8)	(7.8–14.1)	(7.3–12.1)	(6.4–11.4)	(6.8–10.7)	(5.8–10.3)
0.300 mg kg^{-1}	9.1	9.1	7.5	6.7**	5.4**
(n = 6)	(5.0–11.7)	(4.9–9.6)	(4.9–9.0)	(4.7–8.3)	(4.4–6.5)
Vasopressin (pmol L^{-1})					
Placebo	14.1	14.6	16.7	14.9	16.9
(n = 8)	(13.0–18.1)	(13.0–23.8)	(11.9–23.8)	(13.2–21.3)	(14.1-18.0)
0.075 mg kg^{-1}	14.4	15.7	15.1	15.4	16.7
(n = 7)	(11.0–20.1)	(13.4–17.7)	(12.2–15.8)	(9.6–16.6)	(14.8-17.2)
0.150 mg kg^{-1}	15.3	16.2	15.9	14.7	17.3
(n = 8)	(13.8–21.0)	(14.9–19.3)	(12.5–23.7)	(12.3–18.0)	(14.9-19.4)
0.300 mg kg^{-1}	14.7	20.3	14.4	14.4	15.9
(n = 6)	(13.2–21.7)	(14.6–20.7)	(12.5–18.5)	(12.3–16.0)	(14.6-20.5)

Medians with 1st and 3rd quartile in parentheses. *$P \leq 0.05$ and **$P \leq 0.01$ within groups.

decreased equally and significantly in all four groups, but there were no significant differences between the relative changes from basal values to final values in any of the groups.

No other significant changes were observed in the other parameters.

Discussion

The present study has shown that acute infusion of FK-506 to pigs increased mean arterial blood pressure and decreased fractional lithium excretion in the highest dosage groups. Angiotensin II decreased in the placebo group and the two lowest dosage groups but not in the highest dosage group. Otherwise renal haemodynamics and the other vasoactive hormones were only slightly affected by FK-506.

FK-506 has been shown to exert immunsuppressive properties both in humans and in animal models. In the present study pigs were chosen because the cardiovascular and renal systems of the pig are more similar to humans than these systems in rats (Terris 1986). In contrast to the unipapillary kidney in rats, pigs have a polypapillary kidney with predominantly short looped nephrons similar to humans. Thus our pig model offers an opportunity to investigate the acute effects of FK-506 on renal function in a kidney model resembling the human kidney. Furthermore, we have chosen to investigate the non-transplantated kidney in order to avoid any interference from rejection episodes. We chose a dosage range which encompassed dosages previously reported to be immunsuppressive, when given daily both to humans and to animals including pigs (Ochiai et al 1987). In a recent study, FK-506 was shown to prevent skin-allotransplantation in rats only in a very high dosage (0.8 mg kg^{-1} day^{-1}); however in this study FK-506 was administered intraperitoneally (Nielsen et al 1995).

Several chronic studies have shown that FK-506 can reduce renal haemodynamics and might possess some of the same side-effects as cyclosporin A (Kumano et al 1992; Textor et al 1993; The US FK-506 Liver Study Group 1994; Nielsen et al 1995). Information regarding the acute effects of FK-506 on renal function and blood pressure and the mechanism behind the renal side effects of FK-506 is however very limited. In a study in rats acute infusion of 0.384 mg kg^{-1} h^{-1} did not change renal and systemic haemodynamics, whereas continued infusion of 1, 2.5 and 5 mg kg^{-1} day^{-1} for 21 days decreased

creatinine clearance in a dose-dependent manner (Kumano et al 1992). In a recent study (Nielsen et al 1995), 4 weeks of chronic infusion of FK-506 also decreased GFR in a dose-dependent manner, whereas no information was given regarding the acute effect of FK-506. Surprisingly, in our study we found a tendency to an increase in GFR in the two highest dosage groups, but the changes were small and may have been by chance. In addition we did not find any changes in renal plasma flow even in the highest dosage group. Thus, the effect of FK-506 on renal haemodynamics was absent or very modest in the present set-up. However, the acute decrease in FE_{Li} in the two highest dosage groups observed in the present study may suggest that FK-506 have a direct effect on tubular lithium and sodium handling.

Development of hypertension is another known side-effect to Cyclosporin A treatment and has also been reported in FK-506-treated patients (Starzl et al 1990), although the incidence might be less pronounced. The mechanism is unknown. Our analysis did not reveal signs either of sodium retention, since urinary sodium excretion was unchanged, or of hormone-induced vasoconstriction, since the vasoactive hormones ANP, angiotensin II aldosterone and vasopressin also were reduced or unchanged equally in all groups. Our findings of an acute increase in MBP and a decrease in FE_{Li} is thus in good accordance with previous findings and may suggest that FK-506 increases blood pressure together with an alteration in the renal handling of sodium and water. However, an additional vasoconstrictive effect on the arterioles is also possible. Only long-term studies can reveal the mechanisms of the chronic nephrotoxic effect of FK-506.

In conclusion, acute infusion of FK-506 to pigs does not change overall renal function significantly, but increases mean arterial blood pressure and decreases fractional excretion of lithium. The effect of FK-506 on proximal tubular function may result in sodium retention and subsequently hypertension during chronic treatment.

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