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Acute Hemodynamic Effects of FK 506 During and After Orthotopic Liver Transplantation

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THE introduction of Cya was a major breakthrough in organ transplantation. However, side effects of the drug, such as frequent episodes of rejection, nephrotoxicity, and hypertension, stimulated a search for agents devoid of such effects. A recently developed drug, FK 506, appears to be superior to CyA in immunosuppression, with an advantage in humans of minimal side effects.[1] Its reported effects on the cardiovascular system are variable, ranging from no organic change[2-4] to vasculitis and myocardial necrosis.[5] The organic changes seen in animal studies may have been species specific.

This study was designed to investigate the acute hemodynamic effects of FK 506 in patients receiving a large loading dose followed by a maintenance dose.

MATERIALS AND METHODS

This study was approved by the Institutional Research Review Board, and informed consent was obtained from the patients. Sixteen adult patients undergoing primary orthotopic liver transplantation were studied. Anesthetic management followed the standard care at Presbyterian-University Hospital (Pittsburgh, PA). Anesthesia was induced with thiopental and maintained with isoflurane and fentanyl. Electrocardiograms (ECGs) were continuously recorded by a data acquisition system. Complete hemodynamic profile and biochemical variables, including arterial blood gas tensions, electrolytes, ionized calcium, glucose, and lactate, were measured. In addition, right ventricular ejection fraction was measured with a REF-ejection fraction/cardiac output computer (Baxter, Irvine, CA). Standard surgical procedure was followed, including the use of veno-venous bypass. Methylprednisolone (1 g) was given after reperfusion of the grafted liver. During biliary reconstruction, a loading dose of FK 506 (0.15 mg/kg) was infused over 1 hour. This was the first dose of intravenous FK 506 given, as well as the largest. Postoperatively, maintenance doses of FK 506 (0.075 mg/kg) were administered over 1 hour, every 12 hours.

Intraoperatively, a complete hemodynamic profile and set of biochemical measurements were obtained 5 miriutes and 1 minute before, and 15 minutes (FK + 15), 30 minutes (FK + 30), 45 minutes (FK + 45), 60 minutes (FK + 60), 90 minutes (FK + 90), and 120 minutes (FK + 120) after the start of the first FK 506 infusion. Postoperatively, a hemodynamic profile was measured prior to and immediately after a maintenance dose of FK 506 infusion.

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Data are presented as mean ± SD. They were analyzed by analysis of variance, and specific difference were assessed using the Student-Knewman-Keuls test. A value of $P < 0.05$ was considered statistically significant.

RESULTS

The average age of recipients was 37.7 ± 13.9 years, and no patient required vasopressor support other than a small dose of dopamine ($\leq 2\,\mu g\,kg^{-1}\,min^{-1}$) given to 12 patients to improve renal perfusion.

Intraoperative Loading Dose

In three patients, data were available only up to 90 minutes after the start of FK 506 infusion because the operation had ended by that time. The only biochemical changes observed during the study period were a minimal increase in pH and decreases in pCO_2 and pO_2 seen 120 minutes after the FK 506 infusion. Other variables remained unchanged and they were all within the normal range for this patient population (Table 1). No supraventricular or ventricular dysrhythmia was observed on the ECG recordings. Measured hemodynamic variables showed no significant change during the 2-hour period (Table 2).

Postoperative Maintenance Dose

No dysrhythmia was associated with FK 506 administration. The hemodynamic profile was similar before and after infusion of FK 506 (Table 3).

DISCUSSION

The results indicate that infusion of FK 506, both a large loading dose given during surgery and a maintenance dose given during the postoperative period, is not associated with acute cardiovascular effects or hemodynamic compromise. Bolstered by these negative results, this new drug has been used in four heart recipients and in one heart/lung recipient without clinically significant side effects. Further studies are needed to evaluate chronic effects of FK 506 in organ transplantation recipients.

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Table 1

Biochemical Profile Before, During, and After Administration of a Loading Dose of FK 506 (0.15 mg · kg^{-1})

	Before FK 506	FK + 15	FK + 60	FK + 120
pH	7.37 ± 0.04	7.39 ± 0.03	7.40 ± 0.05	7.41 ± 0.05*
pCO_2 (mmHg)	39 ± 5	38 ± 4	37 ± 3	36 ± 3*
pO_2 (mmHg)	270 ± 44	266 ± 39	248 ± 48	231 ± 61*
Base excess (mmol · L^{-1})	−2.6 ± 2.7	−1.9 ± 2.0	−1.6 ± 3.2	−1.5 ± 3.3
Na (mmol · L^{-1})	137 ± 5	139 ± 4	139 ± 5	139 ± 5
K (mmol · L^{-1})	3.5 ± 0.5	3.4 ± 0.4	3.5 ± 0.4	3.5 ± 0.4
Ca^{++} (mmol · L^{-1})	1.07 ± 0.11	1.04 ± 0.11	1.00 ± 0.09	1.00 ± 0.10
Glucose (mg · dl^{-1})	204 ± 47	210 ± 60	229 ± 73	226 ± 63
Lactate (mmol · L^{-1})	5.8 ± 2.4	5.6 ± 2.5	5.0 ± 2.6	5.1 ± 2.7

Note: Values are mean ± SD.

* $P < 0.05$ compared with baseline values.

Table 2

Hemodynamic Profile Before, During, and After Administration of a Loading Dose of FK 506 (0.15 mg · kg^{-1})

	Before FK 506	FK + 15	FK + 30	FK + 60	FK + 120
MAP	77 ± 10	77 ± 8	77 ± 9	76 ± 9	78 ± 11
HR	96 ± 14	93 ± 13	92 ± 13	93 ± 14	93 ± 15
MPAP	19 ± 4	18 ± 4	18 ± 4	19 ± 4	20 ± 4
RVSP	36 ± 7	37 ± 10	35 ± 9	35 ± 10	37 ± 9
RVDP	8 ± 5	9 ± 5	8 ± 5	9 ± 5	9 ± 5
PCWP	10 ± 4	11 ± 4	11 ± 3	11 ± 3	11 ± 2
CVP	10 ± 4	10 ± 4	10 ± 4	10 ± 3	11 ± 3
CI.	4.5 ± 1.4	4.4 ± 1.5	4.3 ± 1.4	4.4 ± 1.5	3.9 ± 1.5
SVI	48 ± 16	48 ± 18	47 ± 15	48 ± 16	43 ± 18
RVEF	50 ± 9	48 ± 11	48 ± 9	48 ± 10	46 ± 10
LVSWI	43 ± 15	43 ± 18	42 ± 16	42 ± 15	39 ± 18
RVSWI	6 ± 3	5 ± 4	5 ± 3	6 ± 2	5 ± 3
SVRI	1317 ± 539	1368 ± 514	1376 ± 444	1337 ± 465	1580 ± 704
PVRI	167 ± 95	163 ± 101	155 ± 104	179 ± 114	229 ± 201
BT	34.3 ± 1.0	34.4 ± 1.1	34.4 ± 1.1	34.4 ± 1.2	34.5 ± 1.2

Note: Values are mean ± SD. Hemodynamic profiles remained unchanged during the observation period.

Abbreviations: MAP (mmHg), mean arterial pressure; HR (beat · min^{-1}), heart rate; MPAP (mmHg), mean pulmonary artery pressure; RVSP (mmHg), right ventricular systolic pressure; RVDP (mmHg), right ventricular diastolic pressure; PCWP (mmHg), pulmonary capillary wedge pressure; CVP (mmHg), central venous pressure; CI (L · min^{-1} · m^{-2}), cardiac index; SVI (ml · m^{-2}), stroke volume index; RVEF (%), right ventricular ejection fraction; LVSWI (g · m · m^{-2}), left ventricular stroke work index; RVSWI (g · m · m^{-2}), right ventricular stroke work index; SVRI (dynes · sec · cm^{-5} · m^{-2}), systemic vascular resistance index; PVRI (dynes · sec · cm^{-5} · m^{-2}), pulmonary vascular resistance index; and BT (°C), body temperature.

Table 3

Hemodynamic Profile Before and After a Maintenance Dose of FK 506 (0.075 mg · kg^{-1})

Variables	Before	After
MAP	95 ± 17	97 ± 18
HR	100 ± 13	101 ± 11
MPAP	19 ± 6	19 ± 5
PCWP	12 ± 5	10 ± 5
CVP	9 ± 3	8 ± 3
CI	5.4 ± 1.0	5.3 ± 0.9
SVI	54.9 ± 14.5	53.2 ± 11.9
LVSWI	62.3 ± 20.9	62.2 ± 15.7
RVSWI	7.5 ± 2.9	7.7 ± 2.6
SVRI	1340 ± 400	1377 ± 338
PVRI	109 ± 50	120 ± 67
BT	36.6 ± 0.6	36.6 ± 0.5

Note: Values are mean ± SD. Hemodynamic profile remained unchanged during the observation period. See Table 2 for definitions of abbreviations.