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The Side Effects of FK 506 in Humans

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An important question about FK 506 concerns the nature and extent of any side effects associated with its clinical use. Because the issues of renal and metabolic effects are addressed in other papers, the discussion here will focus on patient symptoms associated with intravenous and oral FK 506. Since the experience in primarily treated and rescue patients has been so different, the two groups will be described separately. Most of the side effects are associated with intravenous FK 506; taken orally, the drug is associated with few or no symptoms.

PRIMARY FK 506 GROUP

Of 31 patients undergoing liver transplantation and treated primarily with FK 506 and low-dose steroids, 42% had no reported or observable side effects associated with intravenous FK 506, and 87% had no symptoms with oral FK 506 (Table 1). The most common side effects noted with intravenous FK 506 were mild nausea and headache; each symptom was seen in 32% of the patients. No patient in the primary group required antiemetic or analgesic therapy. A curious sensation of warmth or hyperesthesia, either systemic or localized to the extremities, was noted in 23% of patients receiving intravenous FK 506; this effect was not seen with the oral form of the drug. A possible variation of this symptom was circumoral numbness and tingling associated with each intravenous dose; this was seen in three patients (10%), and disappeared with conversion to oral FK 506.

Unusual side effects included tremors, seen in two patients (6%). Itching, flushing, abdominal pain (without clinical sequelae), vomiting, and chest pain (without electrocardiographic changes) were each seen in one patient (3%). Generally, most symptoms began about 30 minutes after the beginning of the intravenous dose and lasted for about 1 hour after the completion of the infusion.

Only four patients (13%) had any symptoms associated with oral FK 506. Three patients (10%) complained of insomnia, and this problem disappeared when the dose of FK 506 was reduced. Two patients (6%) noted headache, and two patients had a sensation of “racing.” Tremors, hair loss, and excessive hair growth were each seen in one patient (3%). In general, the few symptoms associated with oral FK 506 were of minor significance and tended to disappear following dose reduction.

RESCUE FK 506 GROUP

Thirty-one patients receiving FK 506 as rescue therapy after liver or kidney transplantation were studied. The rescue protocol called for both intravenous CyA and FK 506 to be administered on successive days. The greatest number and the only significant side effects were seen during this conversion to intravenous FK 506 (Table 2), when patients had therapeutic blood levels of CyA. Every patient in the rescue group had one or more symptoms

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associated with intravenous FK 506. Seventy-seven percent had headaches of varying severity; during the period of the trial in which combined intravenous CyA and FK 506 were given, most patients needed no analgesic therapy, while the first few patients actually required narcotics. Nausea was also a common side effect and was seen in 65% of patients; again, antiemetics were only required in the first few patients who had received high doses of intravenous CyA and FK 506. Vomiting or diarrhea were less common and were seen in 35% of patients.

The sensation of warmth or hyperesthesia was seen in 61% of the patients receiving intravenous FK 506 as rescue therapy. Less common side effects were flushing or itching, seen in 16% of the patients, and tremors, noted in 13% of patients. There were a number of side effects noted less frequently. These included rash (10%), chest pain (10%; without electrocardiographic changes or creatine phosphokinase-MB enzyme elevations), acute anxiety (10%), anorexia (6%), shortness of breath (6%; without clinical sequelae), abdominal pain or cramping (6%), night sweats (3%), fatigue (3%), photophobia (3%), and blurred vision (3%).

After conversion to oral FK 506 and elimination of CyA, the range and frequency of side effects declined markedly. Nausea and vomiting were seen episodically in 10% of patients; headaches, diarrhea, anorexia, and a question of hair loss were each seen in 6%. These side effects were sporadic and disappeared within a few weeks. Seventy-four percent of the rescue patients had no side effects after conversion to oral FK 506.

DISCUSSION

FK 506 has relatively few side effects in primarily treated patients. The symptoms thus far have been minor and have been seen for the most part only after intravenous administration of the drug. The most common side effects were headache, nausea, vomiting, and flushing. A significantly higher incidence of these side effects was noted in the rescue group receiving intravenous FK 506, and this, plus the other adverse interactions described elsewhere in this symposium, makes us recommend for fresh cases that FK 506 and CyA not be used together.

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Table 1

Side Effects In 31 Patients Treated Primarily With FK 506

Side Effects	IV (%)	PO (%)
Headache	32	6
Nausea	32	0
Sensation of warmth/hyperesthesia	23	0
Circumoral numbness, tingling	10	0
Tremors	6	3
Abdominal pain	3	0
Chest pain	3	0
Flushing	3	0
Itching	3	0
Vomiting	3	0
Insomnia	0	10
Sensation of racing	0	6
Hair loss	0	3
Increased hair growth	0	3
No symptoms	42	87

Table 2

Side Effects In 31 Patients Treated with FK 506 as Rescue Therapy

Side Effects	IV (%)	PO(%)
Headache	77	6
Nausea	65	10
Sensation of warmth/hyperesthesia	61	0
Diarrhea	35	6
Vomiting	35	10
Rushing	16	0
Itching	16	0
Tremors	13	0
Anxiety	10	0
Chest pain	10	0
Rash	10	0
Anorexia	6	6
Shortness of breath	6	0
Abdominal cramping	3	0
Abdominal pain	3	0
Blurred vision	3	0
Fatigue	3	0
Night sweats	3	0
Photophobia	3	0
Hair loss	0	6
No symptoms	0	74