

FK-506: A Potential Breakthrough in Immunosuppression

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TODAY WE HAVE HEARD the preliminary assessment of a new immunosuppressive drug that has exceptional potential interest. Those who discovered FK-506 in Japan and all of the major workers who have examined its properties shared their information in a remarkable display of generosity and frankness.

The amicable tone for the meeting was set by the original Japanese workers from Fujisawa Co, Ltd, Osaka, Japan, who described how knowledge of cyclosporine's (CyA) action guided their activities. They were looking for a fungus or bacteria that could inhibit interleukin 2 synthesis. Having found *Streptomyces tsukubaensis* in the soil not far from Tokyo, the steps of purification, structure delineation, and testing of the FK derivative proceeded rapidly.

Much of clinical relevance is known about FK-506. It is more potent than CyA on a weight-for-weight basis in in vitro models and when tested in rat and dog transplant models. Under all these test conditions, it is synergistic with CyA. Presumably the same applies with other agents, which opens the immediate possibility that FK-506 could be an effective ingredient of polypharmaceutical therapy in which low doses of the constituent drugs will minimize toxicity. Considerable work has been done both on rats and dogs about the dose-effect relationships of FK-506 alone or given with CyA.

The missing or incomplete information is about toxicity. There is little mortality or morbidity in rats, but dogs vomit and can develop lethal emaciation while receiving FK-506. Widespread vasculitis has been seen in many canine organs including the kidneys, liver, heart, and pancreas, but not in the organs of rats and baboons. The consensus was that these were relatively species-specific findings in the dog.

The pharmacokinetics of FK-506 are not known. The significance of toxic manifestations in dogs and even the lack of these manifestations in other species have not been definable without effective methods to assay the blood and tissue concentration of FK-506. Perfection of a highly sensitive enzyme immunoassay was announced at this meeting by scientists of Fujisawa. This means that the missing information can be filled in quickly during the next few months. Studies of subhuman primates will be particularly important because, if promising, these could premonitor phase I clinical trials.

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