Chronopharmacokinetic Study of a New Immunosuppressive Agent, FK 506, in Mice

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ABSTRACT—Chronopharmacokinetic profiles of a new immunosuppressive agent, FK 506, were examined in mice. FK 506 (1 mg/kg) was given orally at 10 AM (day trial) or 10 PM (night trial) once a day for 7 days. Blood samples for measurement of FK 506 concentration in whole blood were obtained just before and at 1, 2, 3, 4, 6, 8 and 12 hr after the final dosage. The time to maximum concentration was shorter and the maximum concentration was greater in the night trial than in the day trial. These findings suggest that absorption of FK 506 is faster and its blood concentration is higher in the night trial.

Keywords: Chronopharmacology, Immunosuppressant, FK 506

FK 506 is a new immunosuppressive macrolide. Its mechanism of action may be similar to cyclosporine, another immunosuppressive agent. It inhibits interleukin-2 production by T cells and is 100 times more potent than cyclosporine (1). FK 506, like cyclosporine, causes nephrotoxicity, although it is less toxic than cyclosporine (2, 3).

There is increasing evidence demonstrating that blood concentrations of lipophilic agents depend on their time of oral administration (4). The chronopharmacological profiles of cyclosporine, a lipophilic agent, have already been examined (5, 6). These studies showed that blood concentrations of cyclosporine and its toxic effects were greater when it was administered during an active period in rats. FK 506 is fairly lipid soluble and is similar to cyclosporine in its solubility properties (7). Therefore, it is assumed that blood concentrations of FK 506 may also depend on its time of administration. If this is the case, the toxic effect of FK 506 might vary with its administration time during chronic therapy as has been reported for cyclosporine (5, 6). In the present study, FK 506 was given orally to mice once a day at 10 AM or 10 PM for 7 days. Chronopharmacokinetic profiles of FK 506 in the night trial were compared to those in the day trial.

Male STD:ddY mice (Japan SLC, Shizuoka) at 10 weeks of age were maintained for more than 4 weeks under conditions of light from 7 AM to 7 PM and dark from 7 PM to 7 AM with free access to food and water. The mean food intake (MF, Oriental Yeast Co., Ltd., Tokyo) was 5.6 g/24 hr/animal. One hundred and sixty mice were divided into two groups. FK 506 (1 mg/kg suspended in 0.5 ml of saline) was given orally to the first group of mice (n = 80) at 10 AM (day trial) and to the second group of animals (n = 80) at 10 PM (night trial) once a day for 7 days. Blood samples were obtained from the abdominal aorta just before and at 1, 2, 3, 4, 6, 8 and 12 hr after the final dosage of the agent. Ten mice were killed at each sampling point in the day and night trials. The FK 506 concentration in whole blood was measured by an enzyme immunoassay (8). The maximum concentration in whole blood (C_max) and time to maximum concentration (t_max) were determined directly from the concentration-time curve of the mean blood concentration for each group. The area under the whole blood concentration-time curve from 0 to 12 hr (AUC_0-12) was determined using the trapezoidal rule. The results are expressed as the mean±S.E. Data were analyzed by the unpaired Student's t-test.

Mean FK 506 concentrations in whole blood are shown in Fig. 1. The mean blood concentration in the night trial was higher than that in the day trial at 1 hr after administration (during an absorption phase) (night trial: 1.09±0.23 vs. day trial: 0.59±0.18 ng/ml, 0.05<P<0.10). The C_max in the night trial was greater than that in the day trial, but the difference did not reach significance (Table 1). The t_max was shorter and AUC_0-12 was greater in the night trial (Table 1). The mean FK 506 in whole blood rapidly decreased during the elimination phase in
both trials (Fig. 1). FK 506 was not detected in any mouse at 3 hr in the day trial and was detected in just one mouse at 4 hr in the night trial. Thereafter, this parameter increased and the second small peak was observed at 6 hr in the day and night trials. In the night trial, the blood FK 506 concentration at 6 hr was higher, although not significantly, than that at 4 hr.

Previous studies have demonstrated that the absorption of lipophilic agents is faster when they are given orally at night in nocturnal rodents (4). The present study showed that in mice, the $t_{\text{max}}$ of FK 506 is shorter and its $C_{\text{max}}$ is greater when it is administered at 10 PM than when it is administered at 10 AM. These findings suggest that the oral absorption of FK 506 is faster in these nocturnal animals when the agent is administered at night.

Species-related, large variabilities have been observed in the value of the elimination half-life ($t_{1/2}$) of FK 506 [baboon, 9.6 hr (mean); dog, 7 hr; rat, <3 hr] (9). As the numbers of observation points were not enough to calculate the $t_{1/2}$ of FK 506, this parameter was not determined in the present study. However, the mean blood concentrations of the agent rapidly decreased during the elimination phase in the day and night trials, which suggests that the value of $t_{1/2}$ is relatively small in this species. The possibility that the $t_{1/2}$ of FK 506 might also be influenced by the time of administration remains to be determined.

An apparent second small peak in blood FK 506 concentration was observed in the present study. A similar phenomenon has been reported in dogs (7). Such a peak of FK 506 might be accounted for by one or more of the following possible mechanisms: 1) Enterohepatic recirculation of the agent; 2) Precipitation of the agent due to the local environment, such as pH changes, and subsequent reabsorption; and 3) Differential absorption from different segments of the gut.

Nephrotoxicity of cyclosporine is roughly correlated with its blood concentrations (10, 11). Animal studies using rats have shown that serum creatinine elevates dose-dependently during chronic treatment with FK 506 (3). This suggests that the nephrotoxic effect of FK 506 also depends on its blood concentrations. Previous chronopharmacological studies have demonstrated that blood concentrations of cyclosporine and the subsequent toxic effect vary with its administration time (2, 3). As FK 506 concentrations in whole blood varied with the time of dosage in the present study, it is speculated that the toxic effect of the agent might also depend on its administration time. Further studies are needed to examine the administration time-dependent changes in the immunosuppressive and toxic effects of FK 506.

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REFERENCES