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The Pharmacodynamics of Pentobarbital Following FK 506 Therapy

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IMMUNOSUPPRESSANTS are administered chronically with other pharmacological agents such as antihypertensives, antifungals, antibiotics, and steroids. Preliminary studies indicate that FK 506 significantly alters hepatic drug metabolism.[1-3] Alterations in hepatic metabolism of a coadministered drug may affect the pharmacokinetics and pharmacodynamics of the other drug. Thus far, no studies have investigated the effect of FK 506 administration on the pharmacological effect of a concurrently administered drug. The objective of this study was to investigate the effect of various routes of administration and different administration regimens of FK 506 on the pharmacodynamics of pentobarbital.

STUDY DESIGN

Male Wistar rats ($N = 42$) were randomized into one of six treatment groups. Group I received intramuscular saline (0.2 mL) for 7 days. Group II was treated with intramuscular FK 506 (1.3 mg/kg) for 7 days and group III received a single intramuscular dose of FK 506 (1.3 mg/kg). Group IV received oral saline (0.9 mL) for 7 days, while group V was treated with oral FK 506 (4 mg/kg) for 7 days. Group VI received a single oral dose of FK 506 (10 mg/kg). All animal body weights were kept close together at the start of the treatment due to reported age differences in drug metabolism and response.[4] One day prior to the pentobarbital administration, jugular catheters were placed in all animals under light ether anesthesia. The animals were fasted overnight and for up to 4 hours after pentobarbital administration. On the study day, blood (0.4 mL) was drawn to determine the trough FK 506 concentration, and 2 hours after the designated treatment, an IV dose of pentobarbital (30 mg/kg) was administered. The animals were placed on isothermal pads and a blinded observer recorded the sleep time. The sleep time was determined when the animal regained his righting reflex twice within a period of 10 seconds. A blood sample was drawn (0.3 mL) at the time the animals awoke to determine the plasma pentobarbital concentration and liver function tests.

ANALYSIS

FK 506 concentrations in the plasma were measured by ELISA.[5] Pentobarbital concentrations were measured by high pressure liquid chromatography.[6] The liver function tests were performed by standard methods.

The various parameters in different groups were compared by analysis of variance. Dunnett's procedure was used to compare the various groups to the control group. A

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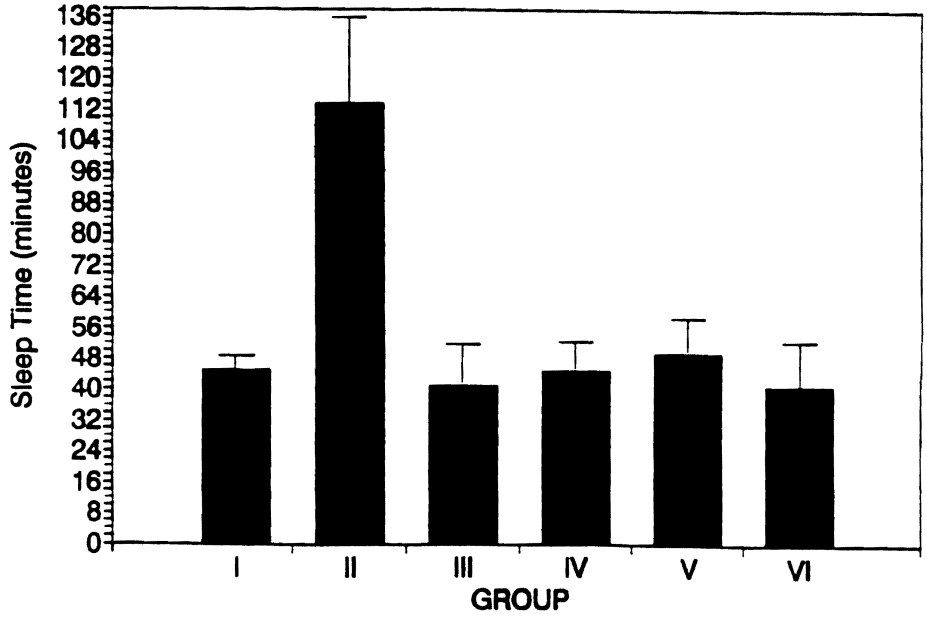

Fig 1. Pentobarbital sleep times: Group I, IM control; group II, IM FK 506 (1.3 mg/kg for 7 days); group III, IM FK 506 (single dose 1.3 mg/kg); group IV, PO control; group V, PO FK 506 (4 mg/kg for 7 days); and group VI, PO FK 506 (single dose 10 mg/kg).

Table 1. Plasma Concentration of Pentobarbital at Wake Up

Group	Concentration (mcg/mL)
I	9.7 ± 2.2
II	10.7 ± 2.8
III	10.3 ± 1.6
IV	11.0 ± 1.9
V	9.7 ± 3.0
VI	10.7 ± 2.5

P value of less than .05 was considered statistically significant.[7]

RESULTS AND DISCUSSION

There were no significant differences in the liver or kidney function tests in all animals, indicating that FK 506 treatment did not alter liver and kidney function in rats.

Sleep times are shown in Fig 1. There was no statistical difference in the sleep time for animals treated with oral FK 506; however, animals which received chronic intramuscular FK 506, on average, slept 69 minutes longer as compared to the control rats. There was no significant difference in the concentration of pentobarbital at the time the animals awoke, indicating that FK 506 treatment did not alter the sensitivity of the central nervous system to the effect of pentobarbital (Table 1).

The trough FK 506 after oral and intramuscular treatment are reported in Table 2. There was no significant difference between the group which received a high single oral dose of FK 506 (10 mg/kg) and the group which received smaller multiple oral doses of FK 506 (4 mg/kg for 7 days), indicating potential accumulation of FK 506 after chronic therapy. Although the concentration of FK 506 was higher in the oral treatment groups as compared to the intramuscular group, there was no change in pentobarbital sleep time when FK 506 was administered orally. This may be partially attributable to the marked fluctuations in the concentration of FK 506 during a dosing interval *after* oral administration, whereas the intramuscular preparation provides a sustained release of FK 506 *during* the dosing interval. It is also possible that FK 506 measured after intramuscular administration is primarily parent FK 506, while following oral administration, more metabolites are produced during the first pass through the liver and the gut which are also measured by the ELISA assay. These metabolites, perhaps, do not alter hepatic metabolism.

Table 2. Trough FK 506 Plasma Concentrations

Group	FK 506 Concentration (ng/mL)
II	9.3 ± 2.0
III	3.7 ± 2.5
V	14.7 ± 9.0
VI	11.6 ± 6.5

CONCLUSIONS

The pharmacodynamics of pentobarbital was affected after chronic intramuscular treatment with FK 506. Since the concentration of pentobarbital was the same at the time the animals awoke in the control group and the chronic intramuscular group, FK 506 does not appear to have altered the sensitivity of the animals to pentobarbital. Although FK 506 is a potent inhibitor of hepatic drug metabolism, as shown by in vitro and in vivo animal studies, chronic oral use of FK 506 in patients is likely to minimally alter hepatic metabolism at clinically relevant doses. Future studies will evaluate the pharmacokinetics of pentobarbital to establish potential changes in the disposition of pentobarbital following various FK 506 treatments.

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