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Steroid Metabolism in Liver Transplant Patients

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LIVER TRANSPLANT patients require chronic administration of immunosuppressive agents to prevent the rejection of transplanted organs. Such therapy usually includes low-dose steroids (prednisone) in combination with cyclosporine.[1] The exact dose of prednisone used is empirically determined and must be balanced between that which is sufficient to maintain graft survival and that which causes minimal side effects. Since the availability and duration of unbound steroid at the receptor site is a determining factor for the time course of its pharmacologic action, a thorough understanding of the pharmacokinetic parameters, such as the rate and extent of absorption, protein binding, tissue distribution, biotransformation, and excretion, is very important.[2] Very little information is available on the pharmacokinetics of prednisone or prednisolone in liver transplant patients. The objective of the present study is to characterize the pharmacokinetics of prednisolone in clinically stable liver transplant patients.

PATIENTS AND METHODS

Ten liver transplant patients (eight females and 2 males) participated in this study. Informed consent was obtained from all subjects prior to the study. The patients fasted overnight and continued to fast for four hours after drug administration. Prednisolone was administered as an intravenous infusion of prednisolone phosphate at a mean dose of 19 mg. Multiple blood samples were obtained over 12 hours after drug administration and plasma was analyzed by a high-pressure liquid chromatographic method.[3,4] Prednisolone binding to plasma protein was determined by equilibrium dialysis. Model independent pharmacokinetic parameters were calculated for prednisolone accoring to standard methods.[5]

RESULTS

All the patients who participated in this study were considered clinically stable based on serum bilirubin concentrations of 2 mg% or less. Table 1 shows the calculated pharmacokinetic parameters of prednisolone. The harmonic mean clearance of total prednisolone was 0.087 (range, 0.053 to 0.113) L/hour/kg. The half-life of predinsolone ranged from 3.1 hours to 5.6 hours in this patient group, with a harmonic mean half-life of 3.9. The harmonic mean clearance of unbound prednisolone was 0.27 (range, 0.18 to 0.66) L/hour/kg, and the half-life was 2.5 hours (range, 2.0 to 4.0).

Table 1. Prednisolone Pharmacokinetics in Liver Transplant Patients

	λ_z* (hr^{-1})	$T_{1/2}$† (hr)	Clearance (ml/min/kg)
Total drug	0.19 ± 0.04	3.8 ± 0.9	0.086 ± 0.022
Unbound drug	0.29 ± 0.05	2.5 ± 0.6	0.33 ± 0.14

*Disposition rate constant
†Serum half-life

DISCUSSION

The mean clearance of total prednisolone in liver transplant patients was approximately 40% lower than that observed in normal subjects. The half-life was also longer in transplant patients, compared to normal subjects. The mean clearance of unbound prednisolone in liver transplant patients was lower than that reported in other subjects receiving prednisolone (0.58, 1.02, and 1.05 L/hour/kg).[6-8]

For drugs that are primarily eliminated from the body by metabolism, a decrease in the unbound clearance indicates a reduced enzymatic activity for elimination of the drug. Our observations indicate that liver transplant patients do not metabolize prednisolone in a manner similar to that of other patient populations. Specific mechanisms responsible for the reduced intrinsic clearance of prednisolone are not clear at this point. It may be a reflection of the reduced steroid-metabolizing activity in the liver. Additional exogeneous factors that may contribute to the decrease in the unbound clearance include the presence of cyclosporine, which has been documented to be an enzyme-inhibiting agent in animal models.[9]

In summary, our studies indicate that a given dose of prednisolone would produce a higher concentration of this drug in liver transplant patients, compared to other patient populations.

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