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Conjugative Drug Metabolism in Liver Transplant Patients

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LIVER TRANSPLANTATION is a therapeutic option for a number of liver diseases.[1] While the kinetics of several drugs are known to be altered in liver disease, very little is known about drug kinetics in liver transplant patients. Since liver transplant patients receive multiple drugs, a thorough understanding of the kinetics of these agents is essential for optimization of drug therapy in this patient population.

Previous studies from our laboratory have shown the oxidative drug-metabolizing capacity of the transplanted liver in clinically stable liver transplant patients to be similar to that of the normal liver.[2] The objective of the present study was to characterize the conjugative drug metabolism of the liver in clincally stable liver transplant patients using acetaminophen (APA) as a model drug.

METHODS

Informed consent was obtained from seven normal and 10 liver transplant patients. After an overnight fasting, the subjects received 975 mg of APA orally along with 200 ml of water. Multiple blood samples were collected over 12 hours and urine was also collected for 24 hours. Plasma was analyzed for APA, and the urine was analyzed for APA, acetaminophen glucuronide (APA-G), and actaminophen sulfate (APA-S) by the high-pressure liquid chromatographic method.[3] Pharmacokinetic parameters such as disposition rate constant (λ_z), disposition half-life ($T_{1/2}$) and the area under the plasma concentration versus time curve (AUC) were calculated according to standard methods.[4] Student's t test was used to determine the presence of significant differences in the various parameters between the normal subjects and the transplant patients.

RESULTS

All but one patient had serum bilirubin concentrations of less than 2.4 mg/dl. The serum creatinine concentrations were less than 1.9 in all but one patient. Table 1 lists the various kinetic parameters calculated from the plasma APA concentration in the two groups studied. There was no significant difference in any of the kinetic parameters calculated between the two groups. The harmonic mean half-life of APA was 2.7 hours (range, 2.1 to 3.6) in normal subjects and 2.8 hours (range, 1.8 to 5.6) in transplant patients. Urinary excretion studies indicate similar amounts of APA, APA-G, and APA-S in the 24-hour urine sample (Table 2).

Table 1. Acetaminophen Kinetics in Normal Subjects and Transplant Patients

Subjects	n	λ_z (hr^{-1})	$T_{1/2}$ (hr)	Clearance (ml/min)
Normal subjects	7	0.258 ± 0.057	2.8 ± 0.6	287 ± 91
Liver transplant patients	10	0.245 ± 0.079	3.1 ± 1.2	263 ± 115

None of the parameters is significantly different between the groups. Significance level: $p < 0.05$.

Table 2. Acetaminophen and Conjugates in Urine

% of Dose Excreted as	Normal Subjects (n = 6)	Transplant Patients (n = 8)
APA	5.3 ± 3.7	8.0 ± 8.4
APA-G	46 ± 10	36 ± 12
APA-S	48 ± 13	56 ± 19

No significant difference in any of the parameters.
Significance level: $p < 0.05$.

DISCUSSION

APA is often used as a model drug to study drug conjugation in humans. Approximately 85 to 95% of the dose administered is converted to the glucuronide and sulfate conjugate and excreted in the urine. Our studies indicate that the transplanted liver conjugates APA to a similar extent when compared to normal subjects. The fraction metabolized to various pathways is similar in transplant patients and normal subjects. This study in conjunction with our previous findings indiciates that the transplanted liver is capable of oxidizing and conjugating drugs in a normal manner. Dosing regimen changes are not necessary in liver transplant patients for drugs eliminated by conjugation pathways.

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