Drug-Binding Proteins in Liver Transplant Patients

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Liver disease impairs the absorption, plasma protein binding, and metabolism of numerous drugs.[1,2] Orthotopic liver transplantation is an accepted therapeutic option for patients with terminal liver failure.[3] The liver is the primary site of plasma protein synthesis. Since a major determinant of the extent of drug binding to plasma proteins is the concentration of the drug-binding proteins, our objective was to measure the concentrations of two primary drug-binding proteins, albumin and alpha-1-acid glycoproteins (AAG), in stable liver transplant patients.

PATIENTS AND METHODS

Fresh heparinized blood (10 ml) was obtained after an overnight fast from 16 stable liver transplant patients (total serum bilirubin ≤ 2.2 mg/dL and serum glutamic oxaloacetic transaminase [SGOT] of less than 40 IU/L), 12 normal healthy adult volunteers, and 7 patients with end-stage liver disease who were being considered for liver transplantation. Blood samples were obtained from transplant patients 21 to 146 days after liver transplantation. Plasma was separated immediately and analyzed for albumin and AAG concentrations. Albumin was measured by bromocresol green dye binding method[4] and AAG was measured by a radial immunodiffusion method with a commercially available kit (ICL International).

RESULTS

The minimum detectable concentration of albumin and the coefficient of variation of the method used are 1 g/dL and 3.1%, respectively. The minimum detectable concentration of AAG and the coefficient of variation of the method used are 20 mg/dL and 5.9%, respectively. A summary of the results obtained is presented in the Table. The mean (±SD) concentration of albumin in the normal subjects was 4.5 ± 0.3 g/dL. This was significantly higher than the albumin concentrations in transplant patients (3.4 ± 0.7 g/dL) and in patients with liver disease (3.4 ± 0.8 g/dL). The mean AAG concentration in normal subjects was 67 mg/dL. Patients with liver disease had a significantly ($P < .05$) lower AAG concentration whereas transplant recipients had a significantly ($P < .05$) higher AAG concentration compared with the normal subjects. Although most of the liver transplant recipients had a twofold higher AAG concentration, one patient had almost a threefold higher AAG concentration than normal subjects.

DISCUSSION

Albumin is primarily responsible for the binding of acidic drugs whereas basic drugs appear to bind preferentially to AAG. The low concentration of albumin and AAG in patients with liver disease indicates the inability of the liver to synthesize these drug-binding proteins. Impaired binding of acidic and basic drugs is well documented in patients with liver disease.[2,5] The albumin concentrations in the transplant patients were low despite stable biochemical liver tests. Because albumin is primarily responsible for binding of acidic drugs, liver transplant patients would not be able to bind acidic drugs as efficiently as the normal subjects. However, the AAG concentrations were elevated in all the transplant patients studied. AAG is an acute-phase reactant and is primarily synthesized in the liver. AAG concentrations are known to increase in plasma after surgery,[6] myocardial infarction,[7] renal transplantation,[8] malignancy,[9] trauma,[10] and inflammatory arthritis.[11] Increased binding of certain basic drugs, such as propranolol[11] and lidocaine,[7] has been ob-

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TABLE

Drug-Binding Proteins in Transplant Patients

Subjects	SGOT (IU/L)	Total Bilirubin (mg/dL)	Albumin (g/dL)	AAG (mg/dL)
Normal subjects (N = 12)	<25	<1.0	4.5 ± 0.3	67 ± 20
Patients with liver disease (N = 7)	42–814	2.0–54.6	3.4 ± 0.8*	46 ± 22*
Liver transplant patients (N = 16)	6–38	0.5–2.2	3.4 ± 0.7*	121 ± 28*

** Significantly different from normal subjects (P < .05).* *AAG = alpha-1-acid glycoprotein.*

served in patients with high AAG concentrations. Therefore, one would also anticipate increased binding of basic drugs in liver transplant patients.

All the liver transplant patients received cyclosporine and prednisone. In addition, some of the patients received azathioprine, hydralazine, hydrochlorothiazide, sulfasalazine, furosemide, or nystatin. These drugs are not known to have specific effects on albumin or AAG concentrations.

Although the binding of certain basic drugs may be higher in liver transplant patients, binding of other basic drugs may not be different from the binding process in normal subjects because of a compensatory reduction in albumin binding. In conclusion, our study has documented the presence of elevated AAG concentrations in stable liver transplant patients. The time course of normalization of these plasma proteins and the binding of different basic drugs should be examined in liver transplant patients.

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