Correlation of Technetium-99m-DISIDA Hepatobiliary Studies with Biopsies in Liver Transplant Patients

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We compared 76 ^{99m}Tc-DISIDA hepatobiliary studies with corresponding liver biopsies in 36 liver transplant patients to determine the histopathologic abnormalities that corresponded to scintigraphic abnormalities in uptake and excretion. Uptake was judged normal if the cardiac blood pool was barely visible or invisible on the ten minute image. Excretion was judged normal if images subsequent to the 15-min image showed a subjectively normal rate of decreasing parenchymal intensity. Biopsies were graded subjectively for hepatocyte damage and for findings of cholestasis. Uptake criteria were successful in differentiating high from low hepatocyte damage scores ($p < 0.0001$), and excretion criteria were successful in differentiating high from low cholestasis scores ($p = 0.002$), while uptake criteria were not capable of differentiating high from low cholestasis scores, nor were excretion criteria capable of differentiating high from low hepatocyte damage scores (p's > 0.05). These results suggest that scintigraphy can distinguish intrahepatic cholestasis from pure hepatocyte damage.

J Nucl Med 1991; 32:1545–1547

Scintigraphy with the IDA derivatives including ^{99m}Tc-DISIDA allows for the separate evaluation of hepatic clearance of tracer from the blood, parenchymal transit, and bile flow through macroscopic portions of the biliary tree (*1*). Several reports have suggested the use of hepatobiliary scintigraphy to detect intrahepatic cholestasis and to separate this entity from other hepatobiliary diseases (*2–5*). These approaches include subjective examination of serial images and quantitative analysis of parenchymal time-activity functions.

Intrahepatic cholestasis appears to be characterized by relatively normal tracer uptake in combination with an abnormally slow decrease in parenchymal intensity but without evidence for obstruction of macroscopic bile ducts. Presumably, in the setting of normal hepatic blood supply, abnormal tracer uptake corresponds to histopathologic evidence for damaged hepatocytes, while abnormal excretion is manifested histopathologically by evidence for cholestasis without a dominant component of hepatocyte abnormality. We tested this hypothesis in a population of liver transplant patients who underwent hepatobiliary scintigraphy and liver needle biopsy as part of their clinical care.

Received Nov. 9, 1990; revision accepted Feb. 12, 1991.

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MATERIALS AND METHODS

Patients

Thirty-six liver transplant patients were included in this retrospective study. Inclusion criteria were: (1) technically adequate scintigraphy; (2) biopsies adequate for interpretation; (3) biopsy and scintigraphy done within 1 wk; and (4) no current clinical evidence for hepatic vascular abnormalities. The mean time between biopsy and scintigraphy was 3.4 days (s.d. = 2.3). The examinations were performed over a 6-yr period. The patients had from one to six (mean = 2.1) hepatobiliary studies and corresponding biopsies. Forty-nine studies were performed routinely in the month following transplantation. Twenty-seven studies were done later to evaluate decreasing liver function.

Scintigraphy

Following injection of six millicuries of ^{99m}Tc-DISIDA, rapid-sequence perfusion images were acquired for 1 min. Anterior images were then obtained at 10, 15, 30, 45, and 60 min. Counts (500,000) were acquired at 10 min; the 10-min and succeeding images were acquired for constant time. A wide field of view gamma camera was used with a low-energy, all-purpose collimator. Scintigrams were evaluated jointly by two experienced nuclear medicine physicians who had no knowledge of the clinical or pathological data. Disagreements occurred in three cases and were settled by discussion and consensus. Tracer uptake was judged normal if the cardiac blood pool was barely visible or invisible on a properly exposed 10-min image. One of the 76 studies was not evaluated for uptake because the cardiac blood pool was not included in the image. Excretion was judged normal if images subsequent to the 15-min image showed a subjectively normal rate of decreasing parenchymal intensity, regardless of the peak parenchymal intensity.

Histopathology

Pathologic specimens used in this study were obtained from needle biopsy; they were formalin-fixed and processed routinely for light microscopy with hematoxylin and eosin staining. Speci-

mens were examined by a pathologist with a special interest in hepatology and who had no knowledge of the clinical or scintigraphic data. Biopsies were systematically evaluated for features of hepatocyte damage and cholestasis. The features of hepatocyte damage were spotty necrosis, central necrosis, and ballooning degeneration. A hepatocyte damage score was defined as the sum of the three separate evaluations of spotty necrosis, central necrosis, and ballooning degeneration, each scored from 0 to 3 (0 = absent, 3 = extensive). The hepatocyte damage score thus potentially ranged from 0 to 9. Cholestasis was judged subjectively on a score of 0 to 3 (0 = absent, 3 = marked). This general score was based on the presence of bile in the lumens of bile ducts, bile ductules and canaliculi, and in hepatocytes and Kupffer cells. A score of 1 represented mild focal bile accumulation in canaliculi and Kupffer cells, and a score of 3 represented widespread accumulation of bile in all portions of the biliary system, Kupffer cells, and hepatocytes.

Statistics

Means and standard deviations were calculated for hepatocyte damage and cholestasis scores corresponding to normal versus abnormal uptake and normal versus abnormal excretion. Independent t-testing was performed on these four pairs of corresponding data.

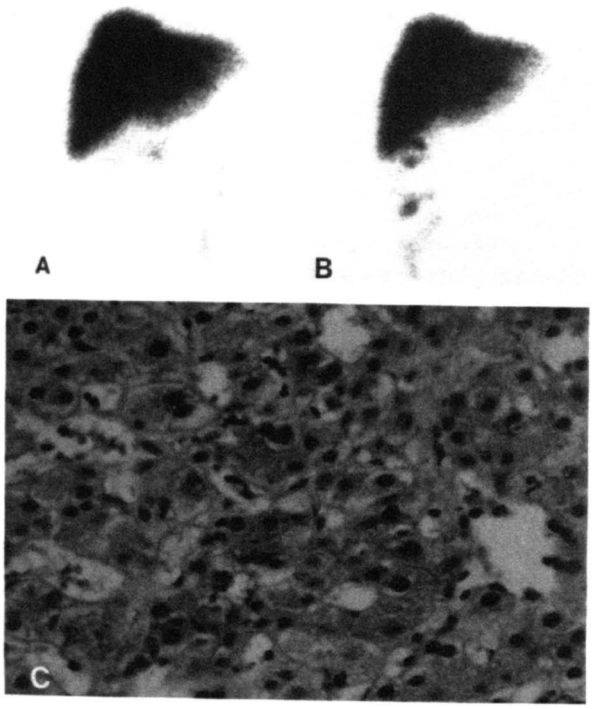

FIGURE 1. The cardiac blood pool is only barely visible at 1 min (A), indicating normal uptake. The 30-min image (B) shows intestinal radioactivity but no decrease in parenchymal intensity from 10 min, indicating severely abnormal excretion. Biopsy (C) shows normal hepatocytes (HD score = 0). Bile collections are seen in hepatocytes, canaliculi, and ductules (CS score = 2). These biopsy findings of normal hepatocytes and cholestasis correspond to the scintigraphic findings of normal uptake and impaired excretion.

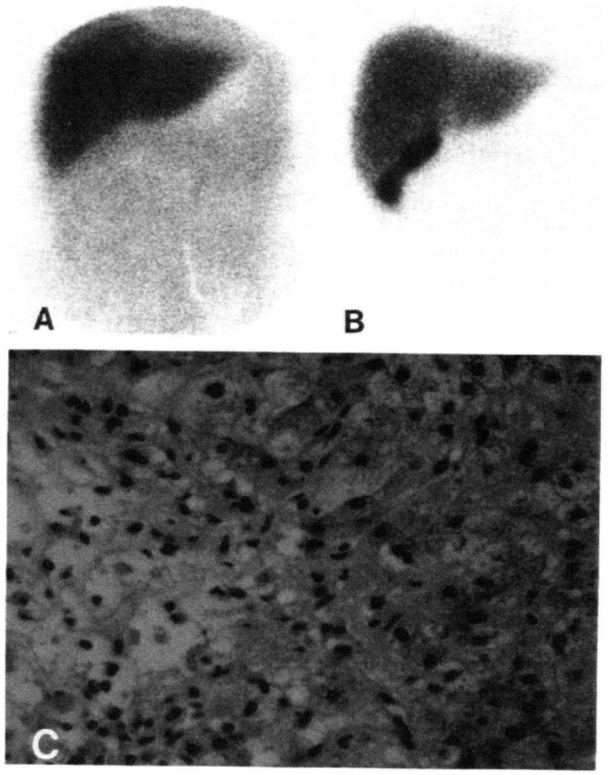

FIGURE 2. The cardiac blood pool is prominent at 10 min (A), indicating abnormal uptake. The 30-min image (B) shows intestinal radioactivity and a decrease in parenchymal radioactivity from 10 min; this decrease is less than expected in a normal liver. These findings suggest moderately impaired excretion. Biopsy (C) shows hepatocyte damage manifested as ballooning degeneration and spotty necrosis (HD score = 6). Only minimal bile stasis is present (CS score = 1). These biopsy findings correspond to the scintigraphic findings of abnormal uptake and excretion.

RESULTS

Sixty-four of the scintigrams were abnormal, 49 had normal uptake but abnormal excretion, and 15 had abnormal uptake and abnormal excretion. Sixty-six of the biopsies showed at least one abnormality, 59 showed evidence of cholestasis, of which 12 lacked evidence for hepatocellular degeneration or necrosis. Seven biopsies showed hepatocellular degeneration or necrosis with no evidence of cholestasis.

Representative scintigrams and biopsies in Figures 1 and 2 illustrate the correspondence between impaired scintigraphic uptake and hepatocyte damage and between impaired scintigraphic excretion and cholestasis. Table 1 summarizes the statistical analysis. This analysis reveals that the mean hepatocyte damage scores associated with normal and abnormal uptake are highly significantly different ($p < 0.0001$). Similarly, the mean cholestasis scores associated with normal and abnormal excretion are significantly different ($p = 0.002$). However, uptake criteria did not significantly separate high from low cholestasis scores

TABLE 1
Mean Cholestasis and Hepatocyte Damage Scores for Normal and Abnormal Uptake and Excretion Groups

	mean CS	s.d.		mean HD	s.d.	
Normal uptake	1.23	1.01		0.97	1.34	
			p = 0.15			p < 0.0001
Abnormal uptake	1.67	1.04		2.93	1.75	
Normal excretion	0.45	0.52		0.64	1.21	
			p = 0.002			p = 0.10
Abnormal excretion	1.49	1.03		1.54	1.73	

CS = cholestasis score; HD = hepatocyte damage score; s.d. = standard deviation.
p-values from t-test.

(p = 0.15), nor did excretion criteria significantly separate high from low hepatocyte damage scores (p = 0.10).

DISCUSSION

Biopsies of transplanted livers frequently show evidence of both hepatocyte damage and cholestasis, although the cholestatic component of the pathology is frequently more dominant (*6,7*). Likewise, abnormalities in excretion as demonstrated by hepatobiliary scintigraphy have been reported as frequent findings in liver transplantation (*4,5*).

We performed this retrospective semiquantitative study to determine whether scintigraphic abnormalities in uptake and excretion correspond to histopathologic evidence of hepatocyte damage and cholestasis respectively. For the purposes of this study, we made the assumption that in a valid model of liver function pure hepatocyte dysfunction is separate from excretory dysfunction. While evidence exists to support this assumption, many pathologic processes very likely result in abnormalities in the capacity of the hepatocyte to extract bilirubin from the blood as well as in abnormalities in bile excretion (*8,9*). Indeed, most of the patients in this study had scintigraphic abnormalities in both uptake and excretion and histopathologic abnormalities in both hepatocyte appearance and bile excretion. This situation may have led to the overlap among categories manifested by the relatively high standard deviations. Nevertheless, the data show a significant correspondence between uptake and hepatocyte injury and between excretion and cholestasis, but not between uptake and cholestasis or between excretion and hepatocyte damage.

The results are potentially corrupted by the lack of truly quantitative data. Quantitative parenchymal time-activity functions were not available in the majority of the examinations included in this retrospective study. Regression analysis to test for correlation between tracer uptake and hepatocyte damage and between tracer excretion and cholestasis would have been interesting, but we judged the image data insufficiently quantitative for such an approach and chose instead the normal versus abnormal grading. While the histopathologic findings could have been quantitated with the measurement of area ratios in the microscopic fields, this approach seemed pointless given the sampling error inherent in needle biopsy applied to a large organ in which the pathology is likely to vary regionally. T-testing must be viewed as an approximate technique when applied to noncontinuous data that may not be strictly parametric.

The value of the results of this study lies in their confirmation of previously suspected and clinically utilized pathologic implications of scintigraphic abnormalities. While the current study did not address rejection specifically, the possibility exists that knowledge of the histopathologic correlates of scintigraphic abnormalities may prove useful in distinguishing rejection from other liver pathology in transplant patients. Further investigation in this area may prove valuable, especially if performed prospectively and with quantitative digital imaging.

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