EDITORIAL

Hepatobiliary Scintigraphy as a Liver Function Test

Hepatobiliary imaging with ^{99m}Tc-IDA derivatives (such as diisopropyliminodiacetic acid or DISIDA) is used to evaluate the integrity of the hepatobiliary system in a variety of disease states. In this issue of the *Journal*, Dogan et al. describe a spectrum of abnormalities encountered in children with cystic fibrosis (*1*). Besides observing the excretion of the radionuclide into the bowel, indicating patency of the draining ducts, an assessment of hepatocyte function is made. A qualitative estimate of liver uptake and clearance is determined from the time-activity curve derived from a region of interest over the right lobe of the liver. With computer acquisition of the data, it is clearly desirable to have an objective measure of liver function. This would hopefully be more sensitive for detecting abnormalities and also allow for comparison of functional changes in sequential imaging.

Several techniques for evaluating hepatocyte clearance have been reported. Gerhold et al. used a visual method (*2*). They compared liver activity to cardiac blood-pool activity in the 5-min image. Clearance was graded on a scale of 1 to 4, where 1 indicated normal clearance (no cardiac blood-pool visible), 2 mild hepatocyte dysfunction (some cardiac blood-pool visible), 3 moderate hepatocyte dysfunction (moderate blood-pool visible) and 4 indicated severe hepatocyte dysfunction (cardiac blood-pool equal to or greater than the liver). This method is obviously subjective and attempts have been made to quantitate this data. El Tumi et al. described a hepatic index as the ratio of the net hepatic-to-cardiac distribution of the ^{99m}Tc-IDA agent between 2.5 and 10 min after injection (*3*). They concluded that an index of 5 or more excludes biliary atresia in infants with hyperbilirubinemia, whereas if it is less than 4.3 atresia is a strong possibility. They could not satisfactorily explain why there was slower uptake of the radiopharmaceutical with biliary atresia. This is in contrast to results from Ohi et al. (*4*) and others who found that patients with neonatal hepatitis, even in the first month or two of life, have severely decreased clearance of the hepatobiliary agent from the blood compared with those having biliary atresia. We have looked at liver uptake 2 and 3 min after injection, expressed as the accumulated liver counts during this period as a percentage of the injected activity, similar to a technique used to quantify renal uptake. These data confirm the better extraction by patients with biliary atresia early in the disease process.

Another method of assessing liver function is based on the generation of time-activity curves. Leonard et al. (*5*) evaluated time-activity curves generated from equal regions over the liver and the heart. The curves were analyzed by nonlinear least-squares curve-fitting procedures. They were visually evaluated and a subjective assessment of liver uptake was made. Again there was good uptake in biliary atresia, but no appreciable hepatic uptake in patients with hepatitis. More sophisticated tracer kinetic studies have been described. Programs have been developed for compartment modeling in nuclear medicine (*6*). Hepatic function with ^{99m}Tc-IDA scintigraphy has been investigated by using these techniques (*7,8*).

Parameters such as rate constants for liver uptake and excretion and mean residence time may be estimated using a three-compartment model. Although there are several assumptions in using the tracer kinetic model, such as using the heart curve as the input function to the liver, which has a dual blood supply, and neglecting the contribution of overlying tissues with planar imaging, these estimates of liver function can be useful in quantitating liver function. Care needs to be taken when bilirubin levels are significantly elevated, since liver uptake is decreased. However, the mean residence time does not seem to be correlated with bilirubin levels, and is perhaps a more useful measure of overall liver function (*7*).

The mean transit time (MTT) of a hepatobiliary agent, such as ^{99m}Tc-DISIDA, has also been measured using a mathematical technique known as deconvolutional analysis. Time-activity curves are obtained from regions over the heart and the right lobe of the liver, excluding ductal activity. The method provides for the simulation of a bolus injection of tracer into the afferent blood supply of the liver from raw data obtained following an intravenous injection.

The MTT has been compared with the results of simultaneously performed BSP determinations and histology under a variety of experimental conditions. Both quantitative imaging and BSP testing could identify milder degrees of hepatic ischemic injury not identified by histology (*8*). Using this same mathematical technique, an extraction fraction has been described. This is the ratio of the y-intercept of the exponential fit to the liver response curve divided by the maximum data value of the response curve. Using this quantitative parameter, as well as the half-time for tracer excretion, it was possible to detect biliary disease and to separate severe hepatocyte dysfunction from biliary tract disease (*9*). Deconvolutional analysis and the determination of the extraction fraction has also been used in pediatrics. As a measure of function, it appears that hepatocellular dysfunction for whatever reason can be separated from biliary atresia in the first 1 to 2 mo of life in patients who fail to excrete the tracer into the bowel (*10*). This is cur-

Received Oct. 5, 1993; accepted Oct. 26, 1993.
For correspondence or reprints contact: Sidney Heyman, MD, Nuclear Medicine/Radiology Dept., Children's Hospital of Philadelphia, 34th St. and Civic Center Blvd., Philadelphia, PA 19104.

rently being evaluated in a prospective manner. Hepatic extraction fraction, and to a lesser extent hepatic clearance time, were also shown to be applicable as a quantitative assessment of liver function in children with a variety of hepatobiliary diseases (*11*).

Still another method for quantitating liver function is to assess receptor biochemistry via kinetic modeling. Technetium-99m-galactosyl-neoglycoalbumin has been validated as a quantitative probe for the hepatic binding protein receptor (*12–14*).

Simple quantitative methods, such as deconvolutional analysis and the extraction fraction, are available with standard software packages. It is suggested that subjective criteria of liver function be supplemented with objective data.

Sydney Heyman
Children's Hospital of Philadelphia
Philadelphia, Pennsylvania

REFERENCES

1. Dogan AS, Conway JJ, Lloyd-Still JD. Hepato biliary scintigraphy in children with cystic fibrosis and liver disease. *J Nucl Med* 1993;35:432–435.
2. Gerhold JP, Klingensmith WC, Kuni CC, et al. Diagnosis of biliary atresia with radionuclide hepatobiliary imaging. *Radiology* 1983;146:497–504.
3. El Tumi MA, Clarke MB, Barrett J, Mowat AP. Ten minute radiopharmaceutical test in biliary atresia. *Arch Dis Child* 1987;62:180–184.
4. Ohi R, Klingensmith WC, Lily JR. Diagnosis of hepatobiliary disease in infants and children with ^{99m}Tc-diethyl IDA imaging. *Clin Nucl Med* 1981;6:297–302.
5. Leonard JC, Hitch DC, Manion CV. The use of diethyl-IDA Tc-99m clearance curves in the differentiation of biliary atresia from other forms of neonatal jaundice. *Radiology* 1982;142:773–776.
6. Marshall EA, Diprose GK, Cosgriff PS. Transport dynamics of the hepatobiliary system: a mathematic model allied to ^{99m}Tc IDA scintigraphy. *Phys Med Biol* 1987;32:719–735.
7. Gambhir SS, Hawkins RA, Huang SC, Hall TR, Busuttil RW, Phelps M. Tracer kinetic modelling approaches for the quantitiation of hepatic function with technetium-99m DISIDA and scintigraphy. *J Nucl Med* 1989;30:1507–1518.
8. Tagge EP, Campbell DA, Reichle R, et al. Quantitative scintigraphy with deconvolutional analysis for the dynamic measurement of hepatic function. *J Surg Res* 1987;42:605–612.
9. Brown PH, Juni JE, Lieberman DA, Krishnamurthy GT. Hepatocyte versus biliary disease: a distinction by deconvolutional analysis of technetium-99m-IDA time-activity curves. *J Nucl Med* 1988;29:623–630.
10. Heyman S, Chapman PR. The extration ratio, initial uptake and visual grading (using Tc-99m DISIDA) in the differential diagnosis of neonatal hyperbilirubinemia [Abstract]. *J Nucl Med* 1990;31:742.
11. Howman-Giles R, Moase A, Gaskin K, Uren R. Hepatobiliary scintigraphy in a pediatric population. Determination of hepatic extraction fraction by deconvolutional analysis. *J Nucl Med* 1933;34:214–221.
12. Kudo M, Vera DR, Trudeau NL, Stadalnik RC. Validation of in vivo receptor measurements via in vitro radioassay: technetium-99m-galactosyl-neoglycoalbumin as prototype model. *J Nucl Med* 1991;32:1177–1182.
13. Ohno K, Itoh K, Nagao K, et al. Clinical application of ^{99m}Tc-DTPA-galactosyl serum albumin in hepatobiliary disease. *Jpn J Nucl Med* 1933;30:217–214.
14. Kudo M, Ikekubo K, Todo A, et al. Hepatic receptor imaging with GSA: estimates of liver function in acute liver disease. *Jpn J Gastroenterol* 1992;89:616–626.