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EDITORIAL

Hepatic Clearance of Technetium-99m-Iminodiacetic Acid Derivatives in Hyperbilirubinemic States

The development of ^{99m}Tc-HIDA (N(2,6-dimethylphenyl-carbamoylmethyl) iminodiacetic acid) by Loberg and coworkers in 1975 (*1*) started a new era in hepatobiliary imaging. Since then, a number of IDA derivatives have been developed, thus allowing the accurate assessment of patency and structural integrity of the biliary tree.

An initial clinical concern was the potential interference of hepatic Tc-IDA uptake by high plasma bilirubin levels. Such concern stemmed from in-vitro work showing competitive inhibition of Tc-IDA uptake by bilirubin in isolated hepatocytes, from studies in dogs showing decreased hepatic clearance of Tc-IDA after infusion of sulfobromophthalein (BSP) and from clinical reports suggesting an inverse relationship between plasma bilirubin levels and hepatic clearance of Tc-IDA (*2–4*). The latter, however, made no distinction between hyperbilirubinemia with and without hepatocanalicular disease.

In 1988, we described a patient with markedly elevated plasma bilirubin levels (about 36 mg/dl), but normal hepatic uptake and excretion of Tc-IDA (*5*). This patient had the Crigler-Najjar syndrome, a hereditary disorder of bilirubin conjugation, but no evidence of parenchymal hepatic disease. Thus, plasma bilirubin per se had no significant effect on the hepatic clearance of Tc-IDA in vivo. This finding, seemingly at odds with earlier thinking, was not necessarily inconsistent with the original in-vitro work, since a number of additional factors, discussed below, are at play in the hepatic clearance of organic anions in vivo. Our report was also consistent with the generally held premise that, in the absence of a conjugation abnormality, secretion into bile was the rate-limiting step in the hepatic clearance of bilirubin and that the hepatic uptake mechanism was not easily saturable in vivo (*6*). Decreased canalicular secretion manifests biochemically as an increase in plasma-conjugated bilirubin, and clinical experience, including our own in biliary atresia, did confirm an inverse relationship between Tc-IDA clearance and conjugated bilirubin levels (*7*).

The report by LeBouthillier and coworkers of a patient with Rotor's disease in this issue of the *Journal* illustrates another rate-limiting factor in bilirubin clearance, namely hepatic storage (*8*). Some aspects of bilirubin metabolism are worth noting for a clearer understanding of the Rotor syndrome and other hereditary hyperbilirubinemias. Circulating bilirubin is taken up by the hepatocyte following detachment of bilirubin from albumin at the sinusoidal plasma membrane. Such uptake is mediated by carrier proteins, including one termed bilirubin translocase. Bilirubin is then bound *reversibly* to binding proteins, for instance y and z proteins and movement across the plasma membrane is bidirectional. Subsequently, bilirubin undergoes conjugation and is then secreted into bile. Technetium-IDA is believed to follow the same general pathway.

The Rotor syndrome is thought to be a disorder of uptake and storage of organic anions (*9,10*). Presumably, a defect in binding proteins leads to increased reflux of (conjugated and unconjugated) bilirubin from the hepatocytes to the plasma, thereby decreasing net hepatic uptake. The reported case, showing prolonged visualization of the cardiac blood pool up to 6 hr, is consistent with this concept. One might argue that the scintigraphic findings in hepatocellular disease, i.e., hepatitis, are similar, but hepatitis severe enough to result in so intense a cardiac blood pool would undoubtedly impair canalicular secretion so that the gallbladder and bowel probably would not visualize, and the liver function test profile would be different.

Much of the information about the specific step(s) of the bilirubin pathway involved in hereditary hyperbilirubinemias has been derived from BSP kinetic studies and our understanding of these disorders continues to evolve. The Rotor syndrome was originally thought to be a variant of the Dubin-Johnson syndrome, a disorder of canalicular secretion, but is now considered a separate pathophysiologic entity primarily involving hepatic storage (*10*). On the other

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hand, the Gilbert and Crigler-Najjar syndromes, originally considered different disorders, may represent varying degrees of severity of the same abnormality, namely decreased conjugation. The possibility of an uptake abnormality, at least in some patients, also exists. Because of the difficulty in characterizing these disorders, many patients with hereditary hyperbilirubinemias are undoubtedly misclassified.

LeBouthillier's report suggests a potential role for Tc-IDA imaging in the hereditary hyperbilirubinemias. In this regard, the development of methods for quantitative compartmental analysis of Tc-IDA appear particularly encouraging (*11–13*). It is hoped that this approach, with appropriate modifications to account for the complexities of bilirubin and Tc-IDA kinetics, will provide additional insight into hereditary hyperbilirubinemias.

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