Scintigraphic Aspect of Rotor's Disease with Technetium-99m-Mebrofenin

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A 28-yr-old male with Rotor's disease was studied with ^{99m}Tc-mebrofenin. The scintigraphic pattern was that of a slow liver uptake with unimpaired excretion and persistent visualization of the cardiac blood pool, kidneys and urinary tract up to 6 hr. The gallbladder was visualized at 55 min postinjection.

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Rotor's disease is an inherited hyperbilirubinemia characterized by the abnormal uptake and storage of bilirubin, resulting in an increased total serum bilirubin mostly of the conjugated form. The use of radioactive dyes such as ^{131}I-Rose bengal and ^{131}I-BSP as well as IDA-derivatives studies have helped understand the pathophysiology of this disease (*1–3*).

We present a case of Rotor's disease studied with the hepatobiliary agent mebrofenin.

CASE REPORT

A 28-yr-old immigrant male originally from Sri Lanka was admitted to our hospital in order to investigate a longstanding (14 yr) jaundice. On admission, he was asymptomatic except for dark urine and occasional pale stools. His father and his brother also had longstanding jaundice. Physical examination was unremarkable except for obvious icteric conjunctivae.

On investigation, CBC was normal as were prothrombin time, serum electrolytes, urea, creatinine, ferritin, α-fetoprotein, creatine kinase, alkaline phosphatase, AST, ALT, amylase, ceruloplasmin, protein electrophoresis and α_1-antitrypsin. Blood glucose was slightly elevated. Total bilirubin was 173 μmole/l (3.4–17.1 μmole/liter), of which conjugated bilirubin contributed 120 μmole/liter. Immunologic testing for A, B and C hepatitis proved negative. Abdominal ultrasound was normal as was the liver biopsy, although the specimen was not subjected to electronic microscopy study. The BSP test did not show any late increment as seen in Dubin-Johnson's disease.

A hepatobiliary scan was performed using ^{99m}Tc-mebrofenin. A dose of 3 mCi was injected. Scintiphotos were obtained immediately following injection and at 5-min intervals for a total of 60 min and then at 3, 5 and 6 hr.

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Figure 1 shows a slow liver uptake with persistent visualization of the cardiac blood pool and prominent kidney excretion up to 6 hr postinjection, at which time intestinal activity is seen. Gallbladder activity is first present at 55 min and gradually increases thereafter.

DISCUSSION

Galli and colleagues (*1*) found that scintigraphic studies differed markedly in Rotor's disease, depending on which IDA-derivative is being used. They showed that with diethyl-IDA, liver uptake was absent at 60 min with only the kidneys and the urinary tract being visualized. Conversely, when parabutyl-IDA was injected, a faint activity was observed in the liver with unimpaired excretion, but the kidneys and urinary tract were not seen.

In clinical studies (*4*), ^{99m}Tc-mebrofenin showed lower renal excretion and no significant difference in hepatic extraction efficiency, time of maximum hepatic radioactivity and hepatic parenchymal washout compared to ^{99m}Tc-diisopropyl-IDA, thus increasing its availability for hepatic extraction.

Our case of Rotor's disease has been studied with ^{99m}Tc-mebrofenin, which showed a slow liver uptake and an unimpaired excretion with the kidneys and urinary tract being visualized throughout the 6-hr imaging interval.

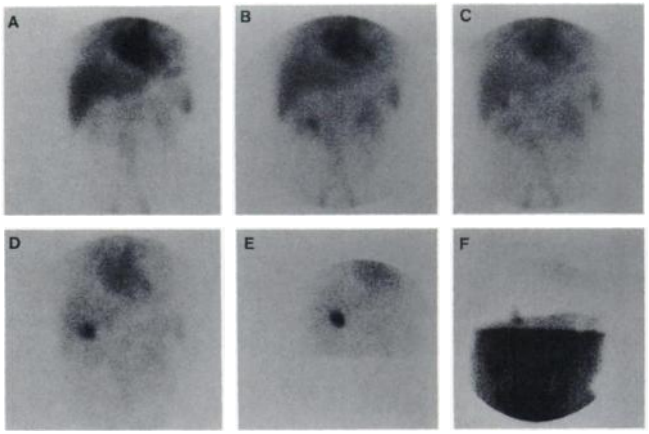

FIGURE 1. Technetium-99m-mebrofenin hepatobiliary scintigraphy (A) immediate, (B) 25 min, (C) 55 min, (D) 3 hr, (E) 6 hr and (F) 6 hr with lead shielding of the upper abdomen in order to demonstrate the presence of intestinal activity.

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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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