Nuclear gastroenterology: novel techniques in clinical and experimental gastrointestinal mobility, IBD and hepatology
Bennink, R.J.

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Chapter 14

Preoperative assessment of liver function:
A comparison of hepatobiliary scintigraphy with the indocyanine green clearance test

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Abstract

Preoperative assessment of liver function is used to estimate the outcome of major liver surgery. The indocyanine green (ICG) clearance test is the most frequently used test for liver parenchymal function but has its limitations. The aim of this study was to investigate the correlation between the liver uptake of $^{99m}$Tc-mebrofenin measured with hepatobiliary scintigraphy and the ICG clearance test.

**Methods.** 54 patients were diagnosed with hepatocellular carcinoma ($n = 9$), hilar (Klatskin) tumors ($n = 20$) and 25 patients with nonparenchymal tumors (NPT) including colorectal metastasis ($n = 15$) and miscellaneous tumors ($n = 10$). Hepatobiliary scintigraphy was performed after intravenous injection of 85 MBq $^{99m}$Tc-mebrofenin, and hepatic uptake rate was calculated. $^{99m}$Tc-mebrofenin hepatobiliary scintigraphy, the 15-min clearance rate of ICG (ICG-C15) and conventional plasma liver function tests were performed 1 day before operation.

**Results.** The ICG-C15 was $86.86\% \pm 1.19\%$ (mean ± SEM). The $^{99m}$Tc-mebrofenin uptake rate was $12.87 \%$/min $\pm 0.52 \%$/min. A significant correlation was obtained between the scintigraphic $^{99m}$Tc-mebrofenin uptake rate and the ICG-C15 ($r = 0.73$, $P < 0.0001$). The mean $^{99m}$Tc-mebrofenin clearance capacity of the right liver segments ($79.83\% \pm 1.63\%$, range 47.75 - 95.97%) was larger than that of the left segments ($20.24\% \pm 1.55\%$, range 6.51 - 52.51%).

**Conclusion.** These data show that $^{99m}$Tc-mebrofenin uptake rate as assessed by scintigraphy correlates well with the ICG clearance and is an efficient method for determining the liver function. At the same time, $^{99m}$Tc-mebrofenin scintigraphy provides information of segmental functional liver tissue, which is of additional value when planning liver resection.
Introduction

Hepatic resection is the therapy of choice for malignant and symptomatic benign hepatobiliary tumors. Recent years have shown a marked decrease in morbidity and mortality rates after major liver resections.\textsuperscript{1,2} Refinements in operative techniques, better selection of patients and advances in perioperative care are thought to be responsible for this improvement.\textsuperscript{3} Nevertheless, perioperative blood loss and postoperative liver failure have remained the most significant complications after liver resections, particularly in patients with suboptimal liver function due to parenchymal liver disease such as cirrhosis or steatosis.\textsuperscript{4} The major cause of mortality after liver resection consequently is liver failure.\textsuperscript{5} For this reason it is important to estimate total and regional liver function before planning partial resection of the liver in order to predict function of the remnant liver.

To date, the most frequently used test for evaluating preoperative liver function is the indocyanine green (ICG) clearance test.\textsuperscript{5,6} ICG is a tricarbocyanine dye, exclusively removed by the liver and excreted into the bile.\textsuperscript{9} The ICG clearance test, requiring intravenous injection and multiple blood samples, provides indirect measurement of global liver function only. Alternatively, $^{99m}$Tc-Technetium ($^{99m}$Tc)-labeled iminodiacetic acid (IDA) analogues, transported in blood by binding to albumin and with a hepatic uptake similar to ICG, can be used for hepatobiliary scintigraphy (HBS) in the assessment of liver function.\textsuperscript{10} In liver transplant patients, HBS has been performed to obtain information about the functional and morphological status of the graft.\textsuperscript{11} HBS, requiring a single intravenous injection, provides visual and quantitative information of global and regional liver function as well as information on excretory biliary function (intrahepatic and extrahepatic bile transport). Both ICG and $^{99m}$Tc-mebrofenin are excreted in bile by the hepatocytes\textsuperscript{12} by the ATP-dependent export pump multidrug-resistance associated protein 2 (MRP 2), without undergoing biotransformation during their transit through the hepatocyte.\textsuperscript{13,14} Therefore, these agents are well suited for the study of hepatic transport. The aim of this study was to examine the correlation of the ICG clearance test with the uptake of $^{99m}$Tc-mebrofenin as determined from the blood as well as from scintigraphical assessment.
Table 1. Patient characteristics

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Materials and Methods

Subjects

Patient characteristics are listed in Table 1. The study group consisted of patients planned to undergo partial liver resection for hepatobiliary tumors between March 2000 and September 2002. Fifty-four patients were included (25 female, 29 male, mean age 59.2 yr, range 37 - 80 yr). Nine patients were diagnosed as hepatocellular carcinoma, 20 as proximal bile duct cancer (Klatskin tumors), 15 as colorectal metastasis and 10 as miscellaneous tumors. Both ICG test and $^{99m}$Tc-mebrofenin uptake and scintigraphy were sequentially performed in patients planned to undergo partial liver resection for primary or metastatic liver tumors or proximal bile duct malignancies. Special attention was paid to additional information obtained from the dynamic scintigraphy images such as possible, local differences detected in liver function or cholestasis of the left- and/or right liver lobes. All patients gave written informed consent to participate in the study, which was approved by the medical ethics committee of the Academic Medical Center of the University of Amsterdam.
Figure 1. Correlation blood clearance

Correlation between clearance at 15 min of ICG and $^{99m}$Tc-mebrofenin (%/15 min; $r = 0.81$, $P < 0.0001$, $n = 36$).

**ICG clearance test**

One day before surgery, bilateral intravenous Venflons™ were placed in the antecubital veins. After an overnight fast, 25 mg of ICG (Infracyanine; Laboratoires pharmaceutiques) was dissolved in 10 mL of 5% dextrose solution and injected rapidly into the antecubital vein. The clearance tests were performed after an overnight fasting because food consumption stimulates hepatic function and bile flow. Blood samples were drawn before the administration of ICG (blank) and at 5, 10, 15 and 20 min after ICG injection. Plasma samples were read against the plasma blank at 805 nm by photospectrometry to determine the concentration of ICG. The theoretical maximum concentration at zero minutes was estimated by using the least squares method. Results were expressed as the percentage ICG cleared at 15 min (ICG-C15 value).
Figure 2. Correlation Blood clearance and liver uptake

Correlation between the $^{99m}$Tc-mebrofenin clearance from blood at 15 min and $^{99m}$Tc-mebrofenin uptake as measured by scintigraphy ($\%$/min; $r = 0.76$, $P < 0.0001$, $n = 36$).

Hepatobiliary scintigraphy

On the same day, all patients underwent hepatobiliary scintigraphy (HBS) using the radiopharmaceutical agent $^{99m}$Tc-labeled (2,4,6 trimethyl-3-bromo) iminodiacetic acid ($^{99m}$Tc-mebrofenin). After intravenous administration of 85 MBq $^{99m}$Tc-mebrofenin (Bridatec; Amersham Health), dynamic image acquisition was performed with a gamma camera (Diacam; Siemens Medical Systems) with the liver and heart in the field-of-view (FOV), using a 128x128 matrix. Dynamic acquisition was performed in 1 h at 10 sec per frame for 60 frames (liver uptake sequence) followed by 50 frames of 1 min (bile excretion sequence). Data was processed on a Hermes workstation (Nuclear Diagnostics). Regions of interest (ROI) were drawn around the liver, the heart and large vessels within the mediastinum (serving as blood pool) and around the total FOV (indicative of total activity). Three different time-activity curves were generated based on the liver, blood pool and total FOV. Liver uptake was calculated in $\%$/min as described
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**Figure 3. Correlation liver uptake and ICG clearance**

Correlation between ICG clearance at 15 min and $^{99m}$Tc-mebrofenin uptake as measured by scintigraphy ($y = 0.2925x - 12.745; r = 0.73, P < 0.0001, n = 54$).

by Ekman,$^{16}$ based on these 3 parameters. Furthermore, ROIs could be drawn around parts of the liver to calculate regional differences in $^{99m}$Tc-mebrofenin uptake. Calculations of $^{99m}$Tc-mebrofenin uptake by the liver were performed using scanned radio activity values acquired between 150 and 350 sec postinjection, to make sure that calculations were made during a phase of homogenous distribution of the agent in the blood pool and before the rapid phase of hepatic excretion.$^{16}$

Since ICG clearance is measured in blood samples, and scintigraphic liver uptake function is measured on planar imaging, additional blood samples were taken to measure $^{99m}$Tc-mebrofenin blood clearance. Blood samples were taken before the administration of $^{99m}$Tc-mebrofenin and at 1, 2, 3, 5, 10, 15, 20 and 30 min after injection.
Figure 4. $^{99m}$Tc-mebrofenin uptake in different tumor types

Box and whisker plots of median values for $^{99m}$Tc-mebrofenin uptake in patients with nonparenchymal tumor (NPT), Klatskin tumor or hepatocellular carcinoma (HCC). Whiskers represent the min-max range of $^{99m}$Tc-mebrofenin uptake, boxes represent the interquartile range (*P < 0.05 by Mann Whitney U test).

By measuring radioactivity in the blood samples, the percentage clearance at 15 min was calculated in the same way as the ICG clearance. For calculating regional liver uptake on hepatobiliary scintigraphy, the global liver ROI was manually divided into 2 parts referring to the right margin of the aorta as the border between the right and left liver lobes.

**Blood plasma analysis**

Blood samples were collected for routine laboratory biochemistry of liver enzymes ALT, AST, LDH, γGT and ALP, and of total and conjugated bilirubin. Routine laboratory chemistry tests were performed to obtain values of albumin, PTT, antithrombin III (AT III) and activated partial tromboplastin time (APTT).
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Figure 5. $^{99m}$Tc-mebrofenin uptake in left and right liver lobes

Box and whisker plots of median (range and interquartile range) values of $^{99m}$Tc-mebrofenin uptake in left and right liver lobes expressed as percentages of total liver uptake. (*** $P < 0.05$ by Mann Whitney $U$ test).

Statistical analysis

Commercial computer package was used for analysis of the data (GraphPad Prism; GraphPad Software). Values are given as mean ± SEM. The relationship between ICG clearance at 15 min and liver uptake of $^{99m}$Tc-mebrofenin was tested using the standard Pearson correlation coefficient $r$. The Mann Whitney $U$ test was used for comparison of data between the groups. All statistical tests were 2-tailed and differences were evaluated at the 5% level of significance.
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Results

The mean ICG-C15 was 86.86% ± 1.19% with a range of 58.51 - 98.32%. The Tc-mebrofenin clearance at 15 min was 83.70% ± 1.72% (n = 36, range 51.80 - 93.20% in 15 min). The Tc-mebrofenin uptake rate was 12.87%/min ± 0.52%/min with a range of 3.2 - 24.4%/min. The ICG-C15 value and the Tc-mebrofenin clearance rate in blood in 15 min showed a significant, positive correlation (r = 0.81, P < 0.0001, Fig. 1). A significant, positive correlation was found between the Tc-mebrofenin clearance rate at 15 minutes and Tc-mebrofenin uptake by scintigraphy (r = 0.76, P < 0.0001, Fig 2). Also, the ICG-C15 value and the Tc-mebrofenin uptake (as evaluated by scintigraphy) showed a significant, positive correlation (r = 0.73, P < 0.0001, Fig 3).

In total, 26 measurements with ICG-C15 above 90% were found. Eleven patients had ICG-C15 values between 86% and 90% and 18 patients had values lower than 86%. The obtained correlation between ICG-C15 and AST was strong. No significant correlation was found between the ICG-C15 values and LDH, APTT and AT III. Moderate correlation was obtained between the ICG-C15 values and conjugated bilirubin (r = -0.49), total bilirubin (r = -0.53), ALT (r = -0.50) and albumin (r = -0.60) in the blood (Table 2).

The median values for Tc-mebrofenin uptake in the patients with various liver malignancies are shown in Figure 4. The median values for Tc-mebrofenin uptake were significantly different between patients in the nonparenchymal tumor (NPT) group (n = 25) and patients with Klatskin tumors (n = 20), as well as between patients in the NPT group and patients with hepatocellular carcinoma (HCC, n = 9, P < 0.05).

The mean Tc-mebrofenin clearance capacity of the right liver lobes (79.83% ± 10.80%, range 47.75 - 95.97%) was larger than that of the left lobes (mean 20.24% ± 10.26, range 6.51 - 52.51%, Fig. 5). Atrophic right or left segments, as was apparent from CT images, had values lower than the mean (data not shown).
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Table 2. Biochemical results

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<td></td>
<td>n</td>
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<tr>
<td>ALT</td>
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Discussion

Prevention of postoperative hepatic insufficiency is important for improvement of the outcome after partial liver resection in patients with malignant liver disease. Patients with hepatic insufficiency after major liver resection have low chances for survival. Therefore, adequate preoperative estimation of liver function potentially improves postoperative morbidity and mortality after major liver resections.

In the literature, the results of ICG tests are expressed as ICG-R15, which describes the percent of retention in 15 min. It has been reported that the ICG-R15 value is a better indicator of liver function than the Child-Pugh classification in patients who underwent cardiac surgery. In these patients, a high ICG-R15 correlated with a high rate of mortality. ICG retention of 14% at 15 min, equaling a clearance of 86% at 15 min, has been suggested as the safe limit for patients undergoing major liver resection. Clinical use of ICG has been associated with a few cases of serious adverse reactions including anaphylactic shock, hypertension, and urticaria. We did not encounter any of these complications during our study.
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Several studies have been performed to estimate the preoperative hepatic functional reserve by making use of $^{99m}$Tc-DTPA-galactosyl human serum albumin ($^{99m}$Tc-GSA) liver scintigraphy. $^{99m}$Tc-GSA is a novel liver scintigraphy agent that binds to the asialoglycoprotein receptor on hepatocytes.\(19\) It was found that the total counts and counts per unit hepatic volume based on $^{99m}$Tc-GSA in the entire liver significantly decreased in patients with more extensive liver disease.\(20\) The disadvantages of $^{99m}$Tc-GSA are that it does not provide any information on hepatic excretory function. For the present study, $^{99m}$Tc-mebrofenin was used because it has high hepatic uptake and fast excretion and it has been shown to have a very low renal excretion.\(21, 22\) Moreover, it can be used at higher plasma bilirubin levels than previous derivatives due to a halogen atom on the phenyl ring.\(21\) It has been demonstrated that uptake of ICG is competitively inhibited by conjugated\(23\) and unconjugated bilirubin.\(24\) In our study this is of less importance because most of the patients underwent decompression of the biliary tract by stenting to reduce serum bilirubin levels before surgery.\(25\) The patients who were not decompressed showed bilirubin values within normal range.

From the ICG blood-time curve and $^{99m}$Tc-mebrofenin levels in blood samples taken during scintigraphy, it was concluded that a mono exponential fit rendered a suitable mathematical model to describe the concentration of circulating radioactivity in the chosen interval. The blood concentration curves of ICG and $^{99m}$Tc-mebrofenin showed the same decline, suggesting the same hepatic uptake rate for ICG and $^{99m}$Tc-mebrofenin (Fig. 6).

To compare clearance of ICG and $^{99m}$Tc-mebrofenin, the clearance rate at 15 min from blood was calculated with the same mono exponential regression analysis. A strong positive correlation coefficient was seen, indicating that the clearance function of the liver was equally represented by both agents.

When the $^{99m}$Tc-mebrofenin clearance rate at 15 min was compared with the uptake rate calculated by using the scintigraphy images, a strong positive correlation was seen. Also, a statistically significant, positive correlation was seen between $^{99m}$Tc-mebrofenin liver uptake by scintigraphy and ICG-C15 levels. These findings indicate that both the blood clearance rate and liver uptake by scintigraphy of $^{99m}$Tc-mebrofenin give a similar estimation of liver function.
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Figure 6. ICG and $^{99m}$Tc-mebrofenin curves in blood after bolus injection

$^{99m}$Tc-Mebrofenin time-activity curve (■) and ICG clearance curves (■■) showing identical dynamic behavior in time.

The results of this study confirm that the standard tests for liver enzymes and bilirubin plasma levels are not appropriate for describing actual liver function in pre-operative patients. When ICG-C15 was compared with the liver enzymes as ALT or ALP, poor correlation was found. Between the ICG-C15 and hepatic synthetic function tests a correlation was observed for albumin and PTT, but not for APTT. Furthermore, the degree of improvement in routine liver transaminase levels was not able to identify clinically improved or unimproved patients with alcoholic hepatitis.

It is known that unaffected liver segments may retain good function and that liver function in cancer-bearing segments tends to be decreased when compared with that of noncancerous segments. Thus, although liver enzymes may be increased due to regional hepatocellular damage, other liver lobes may compensate and establish good liver function.

The correlation coefficient between ICG-C15 and ALT plasma values was lower than between ICG-C15 and AST plasma levels. The discrepancy between the correlations of these transaminases with ICG-C15 can be explained by the localization of the enzymes...
Figure 7. Dynamic hepatobiliary scintigraphy

Dynamic hepatobiliary scintigraphy with 85 MBq $^{99m}$Tc-mebrofenin in a patient with a hilar tumor. Sequential, 5 min images starting at 15 min postinjection. The images show homogenous tracer distribution in the liver (panel A), with excretion into large bile ducts and subsequently, gallbladder and bowel. In segments 7 and 8 stasis of tracer is visualized (panel C-I), corresponding with segmental bile duct obstruction.

within hepatocytes. ALT is localized in the cytosol, whereas AST is found for 80% in mitochondria. Mitochondria are the site of oxidative phosphorylation and are specialized in the production of cellular ATP. A study showed that the hepatic ATP level is reflected by the amount of ICG and excretion of ICG in bile. Severe damage of hepatocytes leads to damage of mitochondria as reflected by the increase of AST in blood, and due to lack of ATP, a decrease of ICG clearance results.
Figure 8. Hepatobiliary scintigraphy

Dynamic hepatobiliary scintigraphy with 85 MBq $^{99m}$Tc-mebrofenin in a patient with cirrhosis. A decreased uptake is depicted in segment 7 and 8 (panel A-I). Gall bladder has been marked out for image quality purposes.

In this study, patients with colorectal metastases (including other liver malignancies in the nonparenchymal tumor (NPT) group) showed a better $^{99m}$Tc-mebrofenin uptake in liver than patients with HCC or patients with a Klatskin tumor. Hepatic changes develop very rapidly after bile duct obstruction. Hepatocyte function can decrease in late stages of biliary obstruction, as is the case in many Klatskin tumor patients, resulting in secondary decline of hepatocyte extraction.$^{31}$ In long-standing cases biliary cirrhosis develops,$^{32}$ which in part explains the decreased $^{99m}$Tc-mebrofenin uptake seen in this patient group. An advantage of HBS is that affected areas of the liver can be seen as not properly visualized areas on the dynamic images obtained during scintigraphy. Another main advantage of scintigraphy over ICG clearance studies is the additional information that
comes with the obtained dynamic images, e.g. visualization of bile pooling in ducts of patients with cholestasis and heterogeneous uptake of the radiopharmaceutical agent in the presence of liver disease.\textsuperscript{11} Moreover, the images may be valuable in separating primary biliary from primary hepatocyte disease.\textsuperscript{22}

HBS has high diagnostic sensitivity in the diagnosis of biliary obstruction during long-term follow-up after curative hepatic resection with biliary-enteric anastomosis. It has proven particularly helpful in diagnosis of segmental biliary obstruction.\textsuperscript{11} Patients with biliary obstruction involving 1 or 2 segments may present with normal or minimally deviating liver function clearance tests. The rest of the liver may function normally.\textsuperscript{15} Scintigraphy allows distinguishing bile pooling in the uptake-image of the corresponding segment. In our study the dynamic images in some of the patients with segmental biliary obstruction showed clearly which parts were affected (Fig. 7).

In our study, for calculating function of the left- and right liver lobes as a percentage of total liver uptake, the right margin of the aorta was taken as the border. This choice was based on the appearance of the aorta in the first dynamic images. In truth, the border is defined by the inferior vena cava. Scintigraphy showed that the right liver lobes had a higher uptake function in comparison with the left lobes. This is in accordance with the larger liver volume of the right liver lobes. It should be noted that the true border between the right and left liver lobes (i.e. the division of segments 5 and 8 on the right side and segment 4 on the left side) corresponds with the caval vein, lying to the right of the aorta, accounting for an underestimation of function of the left liver.

Affected uptake activity of liver segments could be detected by decreased function percentage. Affected liver segments showed decreased uptake activity when compared to the mean value.

Livers with atrophy of the right lobes due to obstruction of the right portal vein as a result of tumor ingrow, showed a decrease in \textsuperscript{99m}Tc-mebrofenin uptake when compared to nonatrophic livers. Cirrhosis present in particular segments of the liver showed decreased activity (Fig. 8). Other studies showed that in diseases like cirrhosis the hepatic extraction, i.e. the portion of the radiopharmaceutical removed during each circulatory pass from plasma, decreases.\textsuperscript{22}
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Following the comparison between ICG-C15 and \(^{99m}\text{Tc}\)-mebrofenin uptake by scintigraphy, an uptake rate of 12.6 %/min could be regarded as the safe limit. It should be noted, that this is a theoretically calculated cut off value.

Conclusion

These data show that \(^{99m}\text{Tc}\)-mebrofenin uptake rate as assessed by scintigraphy correlates well with ICG clearance and is a valid method for determining liver function. Additional morphological information obtained from HBS provides valuable information on localization of liver segments with inferior function and/or bile pooling in obstructed liver segments. Plasma levels of liver enzymes, bilirubin and tests that measure hepatic synthetic function do not correlate well with ICG clearance and are therefore less suitable for assessment of global liver function in patients in need of a liver resection.
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