Cholescintigraphy

MWJ Versleijen, Antoni van Leeuwenhoek, Amsterdam

1. Introduction

^{99m}Tc IDA (iminodiacetate) compounds are rapidly absorbed from the blood by liver parenchymal cells and excreted unchanged via the multidrug-resistance-associated protein (MRP-2) in the bile ducts. In this process, the IDA compound acts as an organic anion. The radiopharmaceutical is transported from the intrahepatic bile ducts to the gall bladder via the right and left hepatic ducts to the common hepatic duct and the cystic duct, if a functioning gall bladder is present, and via the common bile duct to the duodenum. If gall bladder activity is impaired, contraction of the gall bladder can be achieved by cholecystokinin stimulation or a meal rich in fat.
The investigation gives an impression of the function of the liver parenchymal cells, the presence of any obstructions in the intrahepatic or extrahepatic bile ducts, the function of the gall bladder and cystic duct and (spasms of) the sphincter of Oddi. Spasm of the sphincter of Oddi can be detected most effectively using manometry. This invasive procedure can, however, lead to iatrogenic pancreatitis. Enterogastric reflux from the gall bladder to the stomach and leakage of bile into the abdominal cavity after bile duct surgery can also be demonstrated. The investigation can be performed at higher blood bilirubin levels (up to 400 µmol/l) than the levels at which intravenous cholangiography is possible (up to 60 µmol/l).

2. Methodology

This guideline is based on available scientific literature on the subject, the previous guideline (Aanbevelingen Nucleaire Geneeskunde 2007), international guidelines from EANM and/or SNMMI if available and applicable to the Dutch situation.

3. Indications

a. Determination of the total and regional liver function (for example prior to major liver surgery).
b. Acute or chronic cholecystitis. Of severely sick patients, 5-10% may have acalculous cholecystitis, in which cholestasis and thickening of the gall bladder cause ischaemia of the gall bladder wall. This is observed in severely sick patients (sepsis) and as a result of infections (HIV) and conditions associated with decreased gall bladder contractions (diabetes mellitus, parenteral nutrition for more than three months).
c. Suspected obstructive jaundice.
d. Differential diagnosis of neonatal jaundice (hepatitis versus biliary atresia and other congenital biliary abnormalities).
e. Differentiation of biliary dyskinesis: cystic duct syndrome and spasm of the sphincter of Oddi. Cystic duct syndrome can be associated with stasis in the extrahepatic bile duct as a result of a calculus in the cystic duct.
f. Clinical suspicion of bile reflux to the stomach.

g. Clinical suspicion of bile leakage after bile duct surgery.
h. Follow-up after liver transplantation.
i. Differential diagnosis of space occupying lesions (tumour, metastasis, focal nodular hyperplasia and adenoma). For this indication, however, ultrasound, CT, MRI, PET/CT or (rarely) liver colloid scintigraphy (see Liver and Spleen Scintigraphy, pag 323.) are more appropriate.

4. Relation to other diagnostic procedures

a. Ultrasound is the method of choice for investigating suspected obstructive jaundice. The site and cause of the obstruction can also be identified in some cases. Ultrasound-guided cytological aspiration of carcinoma of the head of the pancreas can be performed immediately afterwards. Ultrasound is also the method of choice for investigating a clinical suspicion of acute cholecystitis. Although, the sensitivity and specificity of cholescintigraphy is higher and it can provide additional information if the physical examination and the ultrasound are not conclusive.
b. Bile duct anatomy is visualised most effectively using ERCP or a percutaneous transhepatic cholangiogram.
c. Cholescintigraphy is the method of choice for investigating the clinical suspicion of bile reflux to the stomach or bile leakage into the abdominal cavity after bile duct surgery.

5. Medical information necessary for planning

a. Clinical particulars and tentative diagnosis.
b. Details of any (recent) surgery on the stomach, gall bladder or bile ducts.
c. Blood results: bilirubin, alkaline phosphatase, transaminases and gamma GT.
d. Results of previous imaging, such as ultrasound, abdominal CT, MRI and endoscopic retrograde cholangiopancreatography (ERCP).

6. Radiopharmaceutical

Tracer:	^{99m}Tc-mebrofenin (rapid blood and liver clearance, minimal urinary excretion and more limited sensitivity to hyperbilirubinaemia).
Nuclide:	Technetium-99m
Activity:	50-200 MBq in adults; higher doses (100-370 MBq) may be needed in patients with hyperbilirubinaemia; 2-7 MBq/kg is administered in children, with a minimum activity of 15-20 MBq (37 MBq in neonates with possible biliary atresia since late images (24 h p.i.) are often necessary.
Administration:	Intravenous

7. Radiation safety

a. Pregnancy

The external radiation dose received by the foetus after intravenous administration of the radiopharmaceutical to the mother is approximately 0,65-4,81 mGy (0,013 mGy/MBq). The investigation should be postponed till after parturition whenever possible.

b. Lactation

According to ICRP 106 there is no need to interrupt breastfeeding, but due to

possible free ^{99m}Tc pertechnetate it is advisable to interrupt the feeding for 4 h.

c. *Effective dose (mSv/MBq)*
0,10; 0,045; 0,029; 0,021; 0,017 for respectively a 1-yr-, 5-yr-, 10-yr-, 15-yr old and an adult patient with a normal biological functioning.

8. Patient preparation/essentials for the procedure

Patient preparation

Patients are not allowed to consume any food for at least 6 h prior to the start of the investigation if the clinical query is liver function (standardisation) or gall bladder function. This is not needed for other clinical queries. Children (in particular infants) do not need to fast.

Essentials for the procedure

1. Cholecystokinin (Sincalide or CCK-8 3,3 ng/kg/min for 3 min) or a fatty consumption, such as whole/ full fat (chocolate) milk or a bar of milk chocolate, is required if the clinical query is gall bladder function or if accumulation initially takes place in the gall bladder only, without drainage to the small intestine. Breast milk or formula milk is used as a stimulant in infants.
2. For a differential diagnosis of acute versus chronic cholecystitis morphine (0,04 mg/kg) and Naloxone (antidote) may be used.
3. ^{99m}Tc pertechnetate can be used for localisation of the stomach at the end of imaging to assess whether there was any enterogastric reflux during the investigation.

9. Acquisition and processing

a. Cholescintigraphy can be performed in 3 phases. Phase 1 is always performed; phases 2 and 3 only when indicated.
   - Phase 1: Dynamic images immediately after the injection (30-60 min).
   - Phase 2: Dynamic images after administration of cholecystokinin, a fatty consumption or morphine administration (30 min).
   - Phase 3: Static images for the assessment of bile transport from the intestines or for the assessment of enterogastric reflux after oral administration of ^{99m}Tc pertechnetate. Additional SPECT/CT increases sensitivity and specificity and is particularly useful in patients with suspected biliary leakage.

b. Views: In the dynamic investigation (phases 1 and 2) and the static images (phase 3), anterior images (or anterior-posterior images using a dual-head camera) of the upper part of the abdomen, so the heart, liver, stomach and duodenum are in the field of view of the gamma camera. Positioning: anterior views with the patient in supine position; a right-lateral view with the patient in the left lateral position.

c. If the clinical query concerns liver uptake and liver excretion, dynamic acquisition for 60 min is sufficient.

d. If the clinical query concerns biliary kinetics, the investigation is performed after fasting. Depending on the patient, the gall bladder will have filled by approximately the 30th min postinjection, after which gall bladder contraction can be induced by cholecystokinin or a fatty food/ drink.

e. If the clinical query concerns acute or chronic cholecystitis, the investigation is performed after fasting. If accumulation does not occur in the gall bladder, late images

can be made. An alternative is to administer morphine (0,04 mg/kg subcutaneously) to differentiate between acute and chronic cholecystitis.

f. If the clinical query concerns bile reflux to the stomach, the patient does not need to fast. If accumulation takes place in the gall bladder only, and drainage to the intestine does not occur, the static anterior views must be repeated after intravenous administration of cholecystokinin or after consumption of a drink/food rich in fat. The static images in phase 3 may require the patient to first lie in the left lateral position for some time (10 min) to improve visualisation of bile reflux to the stomach. Views of the left lateral position may then be made (+/- right-lateral views) or once again in supine position (+/-anterior views).

g. If the clinical query concerns biliary atresia in neonates, the investigation is preferably not performed after fasting. Feeding stimulates bile production and makes children somewhat calmer. If clear excretion to the intestine is not visible after 60 min, an extra static image is made after 4 h and if needed after 24 h while continuing food intake as usual in the intervening period. Stimulation of hepatocyte function and biliary excretion by phenobarbital pretreatment (2,5 mg/kg/d twice daily for at least 3-5 days) can increase the specificity of the test.

h. Data processing: In phase 1, the dynamic images are assessed in cine mode and in series. A hepatogram is made in which the gall bladder and the major bile ducts are left outside the ROI; a cardiac time-activity curve provides additional information about the blood-pool activity (and the global liver function). If needed, individual curves either lobe of the liver can be made for the assessment of the regional liver function.

i. In phase 2, the assessment is made based on the dynamic images and the ROI analysis. Gall bladder function can be evaluated by defining a gall bladder ROI and measuring the counts before and after administration of cholecystokinin/ fatty food consumption. The function can be expressed as the ejection fraction (EF) of the gall bladder, defined as:

$$EF = \frac{N_1 - N_2}{N_1} \times 100 \left[\% \right]$$

in which:

N_1 = counts in the gall bladder before i.v. cholecystokinin (or fatty food consumtion)

N_2 = counts in the gall bladder after i.v. cholecystokinin (or fat food consumption)

j. Data recording: Functional images of the dynamic phase can be produced and recorded. Relevant values, including the gall bladder ejection fraction, are recorded.

k. Camera settings and processing

Energy:	^{99m}Tc setting, 140 keV
Window:	15-20%
Collimator:	LEAP
Counting time:	Depending on the indication.
Computer:	For quantification or for digital gamma cameras: In phases 1 and 2, dynamic images of 60 sec per image for 30-60 min, matrix 128×128

In phase 3, static images of 5 min immediately after the dynamic images and/or 4 and 24 h after injection, matrix 256×256.

10. Interpretation

a. If the right and left lobes of the liver demonstrate a significant difference in uptake and excretion, this may indicate an abnormality in the parenchymal cells or an obstruction in one of the lobes.
b. Decreased hepatocyte function results in decreased liver uptake, longer cardiac activity (indication from blood pool) and relatively more excretion in the urine (only in patients with severe insufficiency). Special attention should be paid to liver uptake and excretion in patients with jaundice. Relatively good uptake in combination with slow excretion indicates cholestasis (intrahepatic or extrahepatic). Long-term cholestasis causes secondary damage to hepatocyte function. Poor uptake may prevent a distinction being made, because excretion is almost always decreased in these cases.
c. The 24-h image is often important in cases of neonatal jaundice: some excretion in the intestines is an argument against biliary atresia. Intestinal excretion should be clearly visible in these images to rule out biliary atresia with a high negative predictive value.
d. Various reasons may cause nonvisualisation of the gall bladder. Alongside physiological factors (non-fasting, parenteral nutrition, cholecystectomy), this picture can fit acute or chronic cholecystitis, calculus obstruction, tumour in the neck of the gall bladder or the cystic duct. Differentiation between acute and chronic cholecystitis using cholescintigraphy is more effective after the administration of morphine and the quantification of the increase in activity in the common hepatic duct. The sphincter of Oddi contracts after the administration of morphine and the increased pressure in the cystic duct causes the gall bladder to be visualised only if the cystic duct is patent (chronic cholecystitis, acalculous cholecystitis). In acute cholecystitis and swelling of the cystic duct mucosa, the gallbladder is usually not visualised, even on late images (4 h post injection) or after morphine administration.
e. Cholescintigraphy can differentiate between cystic duct syndrome (CDS) and sphincter of Oddi spasm (SOS) after stimulation with cholecystokinin or a meal rich in fat. Both conditions are associated with a similar clinical pattern of symptoms, but require different treatments. CDS is treated with cholecystectomy. SOS is treated with medication or by performing sphincterotomy; cholecystectomy is contraindicated. In scintigraphy, CDS shows decreased gall bladder ejection fraction with symptoms after stimulation. Alongside symptoms, an SOS has normal gall bladder ejection fraction with filling of the bile ducts (including retrograde) without drainage to the intestines. A normal gall bladder ejection fraction is >35%. Sphincter of Oddi spasm is most accurately demonstrated using a semi-quantitative score including the liver activity peak time (>10 min), the time to initial intrahepatic bile duct activity (>15 min), the time to initial small intestine activity (> 15-30 minutes) and the emptying of the common hepatic duct (<50%, no changes or increase in activity). If drainage to the intestine does not occur, this could indicate common bile duct obstruction.
f. As cholecystokinin is difficult to obtain, whole/ full fat (chocolate) milk, a bar of milk

chocolate or a Boyden meal is recommended. Also, cholecystokinin overdose can cause false negative results

g. Hepatocyte function can be calculated from the first dynamic acquisition and can be a measure of the total or regional liver function. This can provide valuable information when extended liver resection is being considered.

h. A photopenic area indicates a space occupying lesion in the liver. Focal nodular hyperplasia shows increased perfusion, normal uptake and delayed excretion. Adenomas often demonstrate little or no uptake and no excretion. Small abnormalities may be missed. The localisation (posterior, near the gall bladder) can hinder the assessment. Hepatocellular carcinomas can absorb HIDA, depending on the differentiation grade of the tumour.

i. Radioactivity visible in the abdominal cavity indicates bile leakage.

j. Radioactivity visible in the stomach indicates bile reflux to the stomach. The location of the stomach can be verified by oral ^{99m}Tc pertechnetate and an extra image

11. Report

The report should note the accumulation in the liver parenchyma, any differences between the right and left lobes of the liver and drainage via the intrahepatic bile ducts to the gall bladder. It should mention whether there is radiopharmaceutical accumulation in the gall bladder and gall bladder function after contraction as well as drainage via the common bile duct to the duodenum. The blood-pool time-activity curve (of an ROI above the heart) provides additional information about the hepatocyte function.
The occurrence of any enterogastric reflux from the gall bladder to the stomach should also be noted.
Attention should be paid to any drainage of bile to the abdominal cavity and any excretion via the kidneys. In case of decreased liver function renal excretion will increase.

12. Literature

- Bennink RJ, Dinant S, Erdogan D, et al. Preoperative assessment of postoperative remnant liver function using hepatobiliary scintigraphy. J Nucl Med 2004;45:965-71.
- Freitas JE. Cholescintigraphy. In: Ell PJ, Gambhir SS, eds. Nuclear Medicine in Clinical Diagnosis and Treatment, 3rd ed. Edinburgh: Churchill Livingstone; 2004,919-26.
- Kim CK, Yun M, Lim J-K, et al. Refinement of the positive predictive value of gallbladder nonvisualisation after morphine administration for acute cholecystitis based on the temporal pattern of common bile duct activity. Clin Nucl Med 2000;25:603-7.
- Krishnamurthy GT and Krishnamurthy S. Hepatobiliary Imaging in: Nuclear Hepatology. Springer-Verlag Berlin, 2000,104.
- Nadel HR. Hepatobiliary scintigraphy in children. Sem Nucl Med 1996;26:25-42.
- Sostre S, Kallo AN, Spiegler EJ, et al. A noninvasive test of sphincter of Oddi dysfunction in postcholecystectomy patients: the scintigraphic score. J Nucl Med 1992;33:1216-22.
- Turner MA, Fulcher AS. The cystic duct : normal anatomy and disease processes. Radiographics 2001;21:3-22.
- Vera DR, Hoh CK and Méndez J. Scintigraphic measurement of hepatic function. In: Ell PJ, Gambhir SS, eds. Nuclear Medicine in Clinical Diagnosis and Treatment, 3rd ed. Edinburgh: Churchill Livingstone; 2004,847-55.
- Wycherley A. Hepatobiliary function: biliary kinetics. In: Ell PJ, Gambhir SS, eds. Nuclear Medicine in

Clinical Diagnosis and Treatment, 3rd ed. Edinburgh: Churchill Livingstone;2004:837-46.

- Ziesmann H. Functional hepatobiliary disease: chronic acalculous gallbladder and chronic acalculous biliary disease. Semin Nucl Med 2006;36:119-32.
- Sharma P, Kumar R, Das KJ, Singh H, Pal S, Parshad R et al. Detection and localization of post-operative and post-traumatic bile leak: hybrid SPECT-CT with 99m Tc-Mebrofenin. Abdom Imaging 2012;37:803-11.
- Kwatra N, Shalaby-Rana E, Narayanan S, Mohan P, Ghelani S and Majd M. Phenobarbital-enhanced hepatobiliary scintigraphy in the diagnosis of biliary atresia: two decades of experience at a tertiary centre. Pediatr Radiol 2013;43:1365-75.