

Hepatobiliary Imaging With Tc-99m IDA Compounds

1. OVERVIEW

- a) Hepatobiliary scintigraphy is a radionuclide diagnostic imaging study (including planar imaging, SPECT, or hybrid imaging such as SPECT/CT) that evaluates hepatocellular function and the biliary system by tracing the production and flow of bile from the formative phase in the liver, and its passage through the biliary system into the small intestine.
- b) Sequential (or dynamic) images of the liver, biliary tree, and gut are obtained.
- c) Computer acquisition and analysis, including pharmacologic interventions, are used according to varying indications and an individual patient's needs.
- d) These scans often help in the diagnosis of several diseases and conditions, such as gallbladder inflammation (cholecystitis), bile duct obstruction, congenital abnormalities in the bile ducts, such as biliary atresia, postoperative complications, such as bile leaks and fistulas, and assessment of liver transplant

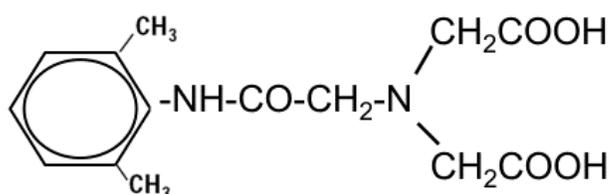
2. RADIOPHARMACEUTICALS UTILIZED

- a) Commercially available kits are available for the preparation of 2 different Tc 99m labeled hepatobiliary imaging agents (Disofenin and Mebrofenin), both of which are iminodiacetate (IDA) derivatives.
- b) They are multi-dose reaction vials which contain the sterile, non-pyrogenic, non-radioactive ingredients necessary to produce Technetium Tc 99m compounds for diagnostic use by intravenous injection.
- c) Each 10 mL multi-dose vial contains the IDA-derivative based compound and stannous chloride (serves as the reducing agent. The pH is typically adjusted to 5.0-5.5 with sodium hydroxide and/or hydrochloric acid prior to lyophilization. No bacteriostatic preservative is present and the vial is sealed under nitrogen.
- d) The two hepatobiliary agents available in the US are listed in the chart below along with their typically prescribed doses. The two currently available drugs are Tc-99m disofenin and Tc-99m mebrofenin.

IMAGING PROCEDURE	RADIOPHARMACEUTICAL ADMINISTERED	INJECTED DOSE (mCi)
HEPATOBIILIARY	^{99m}Tc disofenin (DISIDA)	3-8
	^{99m}Tc mebrofenin (Choletec)	3-8
	^{99m}Tc lidofenin (HIDA) (no longer available)	3-8

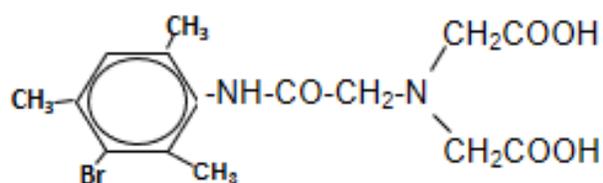
- e) Tc-lidofenin (HIDA) was the first hepatobiliary agent introduced in the US. HIDA only worked well up to a bilirubin level of ~ 8 and therefore was not useful in jaundiced patients. It was soon followed by other compounds that worked well at bilirubin levels in the low 20s. The molecular formula for HIDA is

HIDA

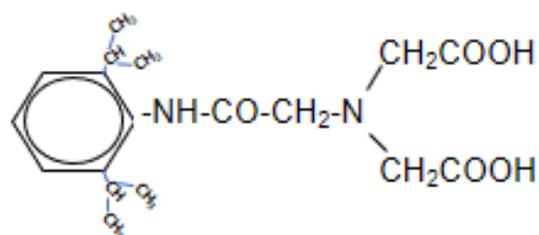


- f) For comparison purposes, the molecular formulas for the two currently available compounds are displayed below. The only difference between all three formulas is different substituent groups on the benzene ring.

MEBROFENIN



DISOFENIN



3. CHARACTERISTICS OF THE RADIONUCLIDE

- a) Tc 99m decays by isomeric transition with a physical half-life of 6.02 hours. The principal photon that is useful for detection and imaging studies has a percent abundance of 89.07 % and the energy is 140.5 KeV.
- b) The specific gamma ray constant for Tc 99m is 0.78 R/millicurie-hr at 1 cm.
- c) The first half-value layer is 0.017 cm of lead (Pb) and the first tenth value layer is 0.08 cm of Pb.

4. DRUG AVAILABILITY

- a) The two drugs listed in the chart above are readily available in the US in the form of unit doses calibrated for a particular patient as well as a “cold kit” that must be reconstituted with Tc-99m pertechnetate prior to use.

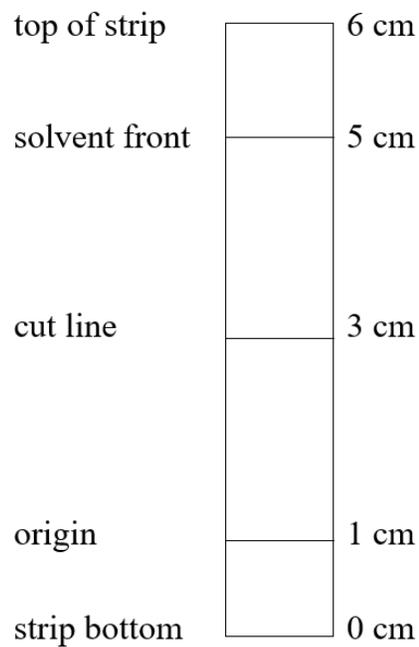
5. DRUG PREPARATION

- a) Waterproof gloves should be worn during the preparation procedure.
- b) With a sterile shielded syringe, aseptically add 1-5 mL of oxidant free, sterile and non-pyrogenic Tc 99m Pertechnetate containing no more than 3.7 GBq (100 millicuries) to the vial.
- c) Swirl the contents of the vial for one minute, and let stand for at least 10 minutes. Record time and date of preparation.
- d) The radiochemical purity of the prepared radiopharmaceutical should be checked prior to patient administration.
- e) Aseptically withdraw material with a sterile shielded syringe for use within six hours of preparation.
- f) The patient dose should be measured in a suitable dose calibration system immediately prior to administration.

6. RADIOCHROMATOGRAPHIC QUALITY CONTROL PROCEDURES

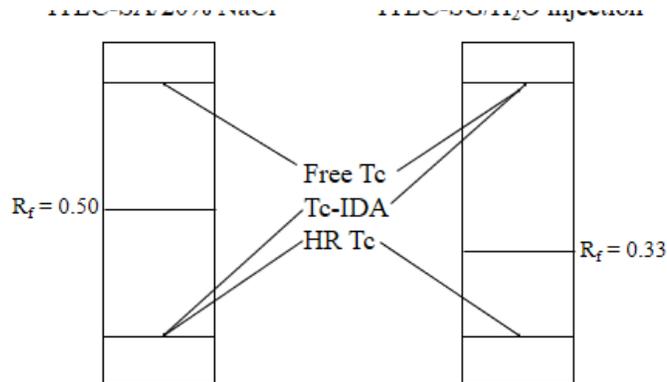
- a) A small drop of the Tc-99m bone agent no wider in diameter than 1/3 the width of the chromatography strip should be placed on the origin line and the strip should be immediately placed in the vial containing the solvent.
- b) Once the solvent has migrated to the line marked “solvent front”, the strip is removed, cut on the “cut line”, and the two halves of the strip are placed in labeled test tubes for counting.

STRIP DESIGN

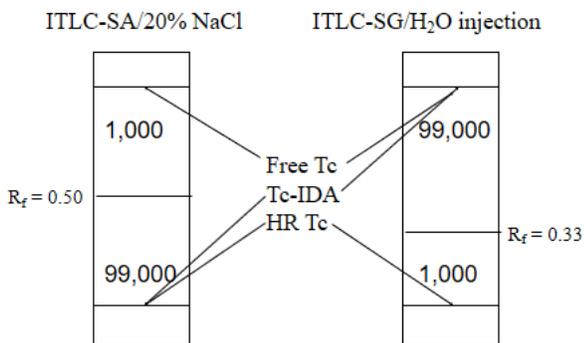


Tc-99m IDA CHROMATOGRAPHY: SEPARATION ON STRIP

<u>SYSTEM</u>	SEPARATION OF RADIOCHEMICAL SPECIES
ITLC-SA/20% saline	Free Tc in top half; all other species in bottom half.
ITLC-SG/water	HR Tc in bottom half; all other species in top half.



What is Radiochemical Purity of Tc-IDA?



Results

$$\% \text{ free Tc} = 1,000 / (1,000 + 99,000) = 1 \%$$

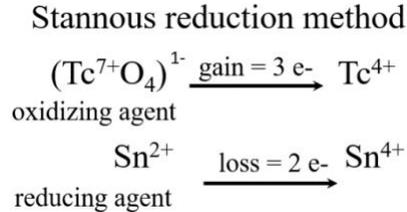
$$\% \text{ HR Tc} = 1,000 / (1,000 + 99,000) = 1 \%$$

therefore,

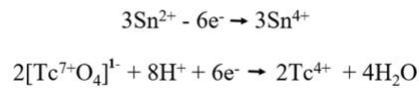
$$\% \text{ IDA} = 100 \% - 2 \% = 98 \%$$

7. RADIOCHEMICAL REACTION

- a) It is necessary to convert the electronegative pertechnetate to an electropositive form as it is unable to react with the electronegative phosphonate compound due to repulsion of 2 negative ions. That conversion of pertechnetate takes place via a reduction/oxidation reaction as shown below.

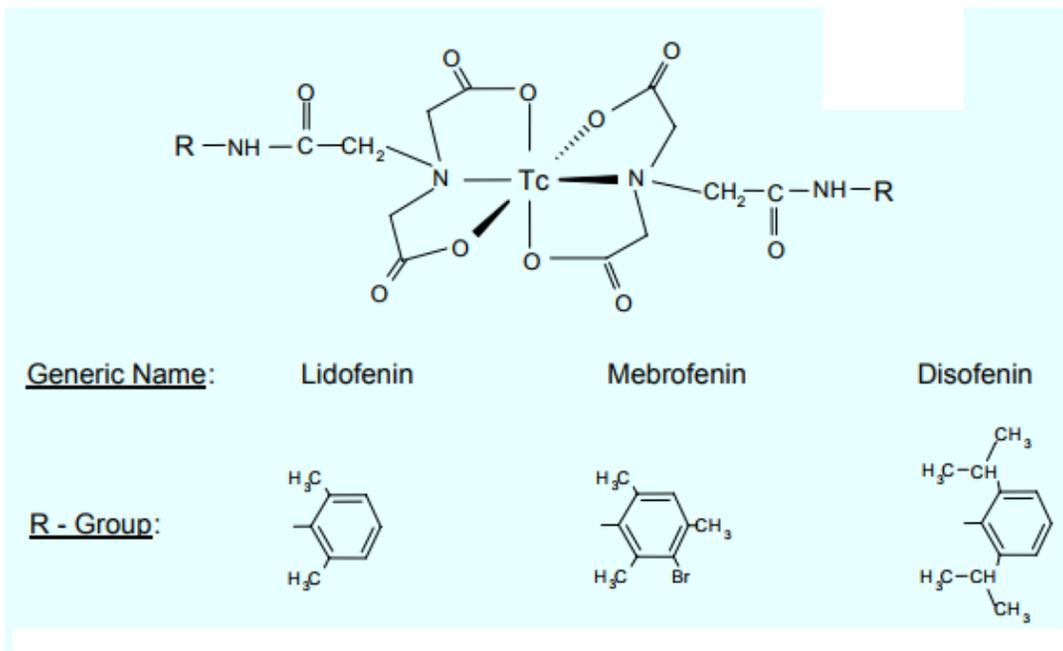


- b) Overall reaction



THEREFORE,

- c) Tc^{4+} then reacts with 2 molecules of the IDA derivative as shown below.
- $$2[\text{Tc}^{7+}\text{O}_4]^{1-} + 16\text{H}^+ + 3\text{Sn}^{2+} \rightarrow 2\text{Tc}^{4+} + 3\text{Sn}^{4+} + 8\text{H}_2\text{O}$$



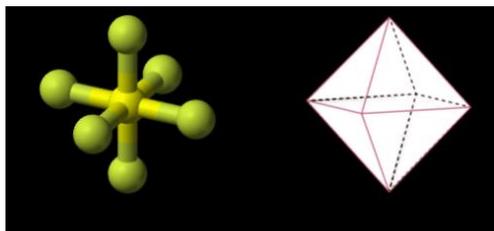
Ref:

https://pharmacyce.unm.edu/nuclear_program/freelessonfiles/Vol12Lesson3.pdf

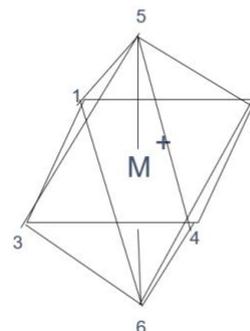
By Richard Kowalsky, Pharm D

- d) The Tc-IDA complex, a hexa-coordinated molecule, has an octahedral structure as illustrated in the diagram below.

In chemistry, octahedral molecular geometry describes the shape of compounds with six atoms or groups of atoms or ligands symmetrically arranged around a central atom, defining the vertices of an octahedron.



**Hexa-coordinated Compound
Octahedral Structure**



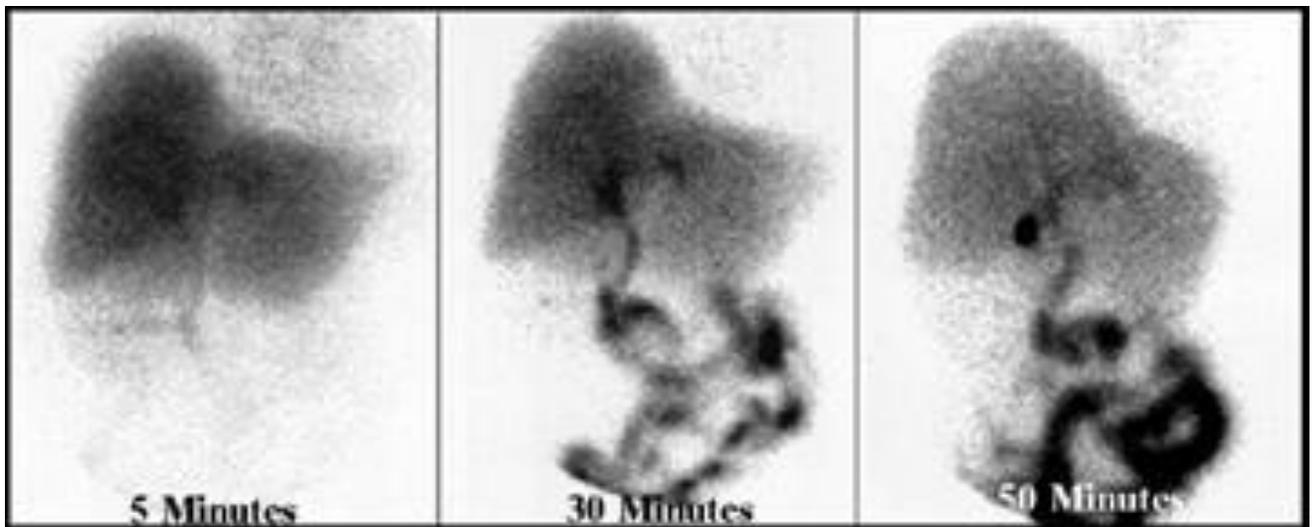
8. CLINICAL PHARMACOLOGY

- a. Mebrofenin is an iminodiacetic acid (HIDA) derivative with no known pharmacologic action at the recommended doses.
- b. Following intravenous administration in normal subjects, Tc 99m Mebrofenin was rapidly cleared from the circulation. The mean percent injected dose remaining in the blood at 10 minutes was 17%.
- c. The injected activity was cleared through the hepatobiliary system with visualization of the liver by 5 minutes and maximum liver uptake occurring at 11 minutes post-injection. Hepatic duct and gallbladder visualization occurred by 10 to 15 minutes and intestinal activity was visualized by 30 to 60 minutes in subjects with normal hepatobiliary function.
- d. The mean percent injected dose excreted in the urine during the first 3 hours was 1% (0.4 to 2.0%). Elevated serum bilirubin levels increase renal excretion of Tc 99m HIDA agents. In two studies in which Tc 99m Mebrofenin was administered to patients having mean elevated serum bilirubin levels of 9.8 mg/dL (1.7 to 46.3 mg/dL), the mean percent injected dose excreted in the urine during the first 3 hours was 3% (0.2 to 11.5%). The mean percent injected dose excreted in the urine during 3-24 hours was 14.9% (0.4 to 34.8%).

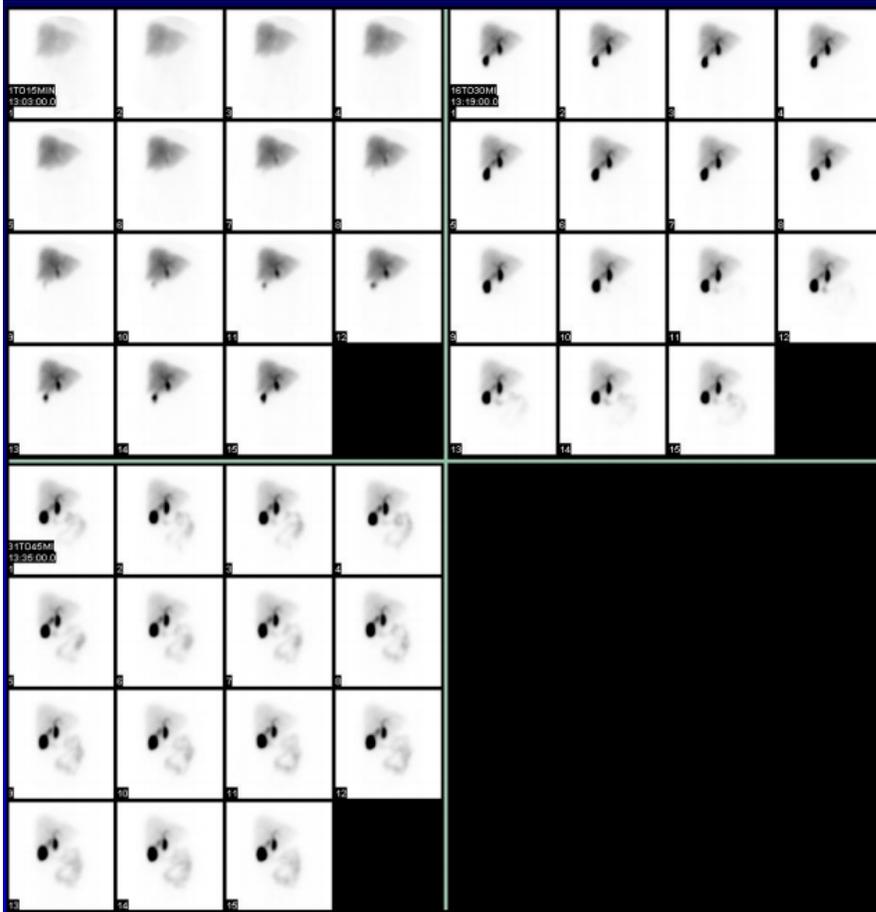
- e. In jaundiced patients, the percent injected dose remaining in the blood at 10 minutes may be twice as high as or more than the level in normals. Hepatobiliary transit may be delayed and visualization times increased. As a consequence, the quality of the images obtained frequently diminishes.

9. NORMAL DISTRIBUTION OF DRUG: 2 EXAMPLES

This case is an example of a normal hepatobiliary scan. The 5-minute image shows normal perfusion of the radiopharmaceutical in the hepatic cells. The 5-minute image shows activity in the myocardium, which is seen above the left lobe of the liver. The 30-minute image identifies activity flowing all the way to the small intestine. At 50-minutes the gall bladder



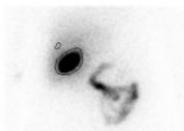
contains radio-bile, indicating that the cystic duct is patent.



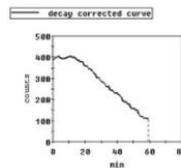
Dynamic images (in sets of 15 minutes, 1 minute per frame) show prompt and uniform uptake in the liver and within 45 mins activity is seen in the biliary tract, gall bladder and the bowel. Patent cystic duct has ruled out acute cholecystitis and the study was shortened to 45 min.



LAO15 CCK INFUSION HIDA @ 4min/frame



INITIAL GALLBLADDER ACTIVITY
GB EF % = 72 @ 50 min



ACO: RB2 / PRO: AL

HIDA Scan

- Normal filling of the gallbladder
- Unobstructed passage of radiotracer through the cystic duct, bile duct and into the duodenum
- Gallbladder ejection fraction of 72% (Normal > 33% for this protocol)

Normal cholescintigraphy (HIDA) scan with no evidence of cholecystitis or gallbladder dysfunction

10. INDICATIONS FOR CLINICAL STUDIES

“[SNMMI Practice Guideline for Hepatobiliary Scintigraphy 4.0]” is reprinted from http://snmmi.files.cms-plus.com/docs/Hepatobiliary_Scintigraphy_V4.0b.pdf, © SNMMI Inc.

- a) Functional biliary pain syndromes in adults
- b) Functional biliary pain syndromes in pediatric patients
- c) Acute cholecystitis
- d) Right-upper-quadrant pain variants, as defined by the Biliary system patency
- e) Bile leakage
- f) Neonatal hyperbilirubinemia (biliary atresia vs. neonatal hepatitis “syndrome”)
- g) Assessment of biliary enteric bypass (e.g., Kasai procedure)
- h) Assessment of liver transplant
- i) Afferent loop syndrome
- j) Assessment of choledochal cysts
- k) Calculation of gallbladder ejection fraction (GBEF)
- l) Functional assessment of the liver before partial hepatectomy
- m) Demonstration of anomalous liver lobulation
- n) Enterogastric (duodenogastric) reflux assessment
- o) Esophageal bile reflux after gastrectomy (72)

p) Sphincter of Oddi dysfunction (73–77)

11. TYPICAL ADMINISTERED DOSE FOR ADULTS

- a) The usual administered activity for adult patients is 3-8 mCi, injected intravenously. The dose is based on the patient's bilirubin level rather than body mass, as it is with most other radiopharmaceuticals.
- b) To determine the dose, one can use the following formula, or can use clinical judgment, taking into account the patient's bilirubin level

Hepatobiliary agents: dose determination
(range = 3-8 mCi)

$$3 \text{ mCi} + \frac{0.5 \text{ mCi}}{2 \text{ bili units elevation}}$$

For example, if bilirubin is elevated 10 units,
 $3 \text{ mCi} + \frac{0.5 \text{ mCi}}{2 \text{ bili units}} \times 10 \text{ bili units} = 5.5 \text{ mCi}$

12. PATIENT PREPARATION FOR HEPATOBILIARY IMAGING

- a) The rationale for performing the procedure and the details of the procedure itself should be explained to the patient in advance.
- b) Unless contraindicated, the patient should be in a fasting state, 4 hours is preferable. False positives (non-visualization) may result if the gallbladder has been emptied by ingestion of food.

13. DRUG ADMINISTRATION PROCEDURE

- a) The injection is performed intravenously over a period of a few seconds.
- b) A small volume of blood is drawn back into the syringe and then re-injected to insure complete delivery of the bone agent.
- c) Hemostasis is accomplished using a gauze pad and pressure.
- d) The gauze pad at the injection site is covered with a Band-Aid or tape.

14. IMAGING PROTOCOLS

Adapted from “[SNMMI Practice Guideline for Hepatobiliary Scintigraphy 4.0]” and reprinted from http://snmmi.files.cms-plus.com/docs/Hepatobiliary_Scintigraphy_V4.0b.pdf, © SNMMI Inc.

Image Acquisition

- a) A large-field-of-view γ -camera equipped with a low energy all-purpose or high-resolution collimator is recommended.
- b) Whenever possible, continuous (dynamic) computer acquisition (usually in the anterior or left anterior oblique view) should be performed (1 frame/min).
- c) The image matrix of 128 by 128 is optimal on a standard large-field-of-view camera. In pediatric patients an appropriate electronic acquisition zoom should be used. Initial
- d) images are usually acquired dynamically, starting at injection and continuing for 60 min. When visualization of the gallbladder is the endpoint of the study, it can be stopped earlier when activity is seen in the gallbladder.
- e) Additional views (e.g., right lateral, left or right anterior oblique) may be obtained as needed to clarify anatomy.
- f) To resolve concern about common bile duct obstruction (highly unlikely in the presence of gallbladder visualization), demonstration of tracer activity in the small bowel may need to be pursued.
- g) The digital data can be reformatted to 4- to 6-min images for filming or digital display. Cinematic display of the data may reveal additional information not readily apparent on reformatted display. Image intensity scaling should be study-relative rather than individual frame-relative.
- h) The former allows for appreciation of activity changes over the duration of the study. When acute cholecystitis is suspected and the gallbladder is not seen within 60 min, delayed images for up to 3–4 h should be obtained, or morphine augmentation (VI.E.2) may be used in lieu of delayed imaging. Delayed imaging at 18–24 h may be necessary in some cases (e.g., a severely ill patient, severe hepatocellular dysfunction, suspected common bile duct obstruction, or suspected biliary atresia).
- i) If the patient is being studied for a biliary leak, 2- to 4-h delayed imaging (or longer delays in some cases) and patient-positioning maneuvers (e.g., decubitus views) may be helpful. Any drainage bags should be included in the field of view if the biliary origin of a leak or fistula is in question. In patients with a suspected leak, it may be helpful to acquire simultaneous right lateral or other views on a multi-head camera.

15. SOURCES OF ERROR

The **causes of a false-positive study** (gallbladder non-visualization in the absence of acute cholecystitis) include:

- a. Insufficient fasting (<2–4 h)
- b. Prolonged fasting (>24 h), especially total parenteral nutrition (despite sincalide pretreatment and morphine augmentation)
- c. Severe hepatocellular disease
- d. High-grade common bile duct obstruction
- e. Severe intercurrent illness (despite sincalide pretreatment and morphine augmentation)
- f. Pancreatitis (rare)
- g. Rapid biliary-to-bowel transit (insufficient tracer activity remaining in the liver for delayed imaging)
- h. Severe chronic cholecystitis
- i. Previous cholecystectomy

The **causes of a false-negative study** (gallbladder visualization in the presence of acute cholecystitis) are rare but include:

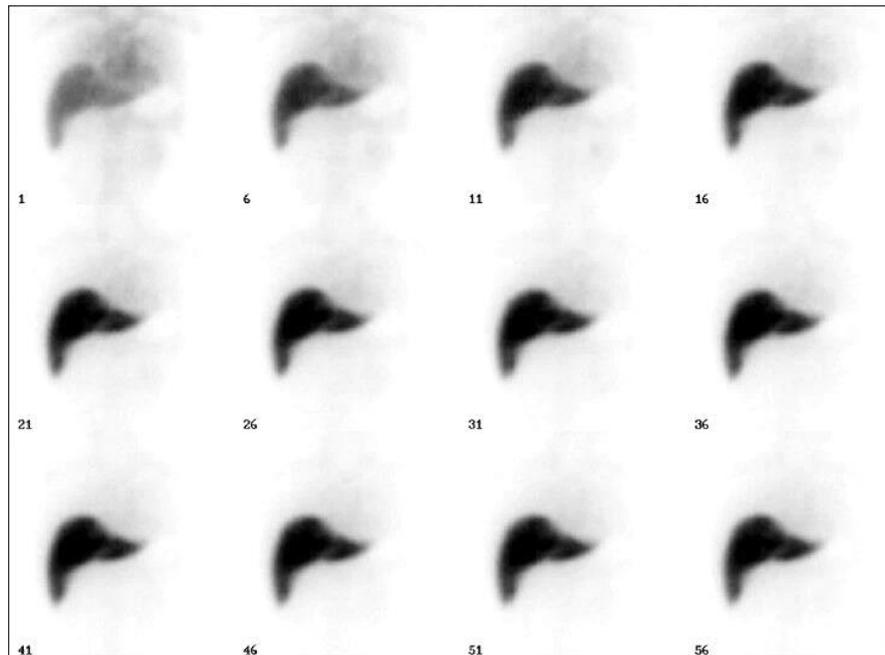
- a. A bowel loop simulating gallbladder (Drinking 100–200 mL water may remove the radiopharmaceutical from the duodenum and allow differentiation of gallbladder from bowel. Review of dynamic images in a cine display may also be helpful. A right lateral view should be obtained to better distinguish activity in the duodenum from that of the gallbladder.)
- b. Acute acalculous cholecystitis
- c. The presence of the dilated-cystic-duct sign simulating gallbladder (If this sign is present, morphine should not be given.)
- d. A bile leak due to gallbladder perforation
- e. Congenital anomalies simulating the gallbladder
- f. Activity in the kidneys simulating the gallbladder or small bowel (may be clarified by a lateral image)

16. ADVERSE REACTIONS FOLLOWING IV INJECTION OF Tc-LABELED IDA DERIVATIVES

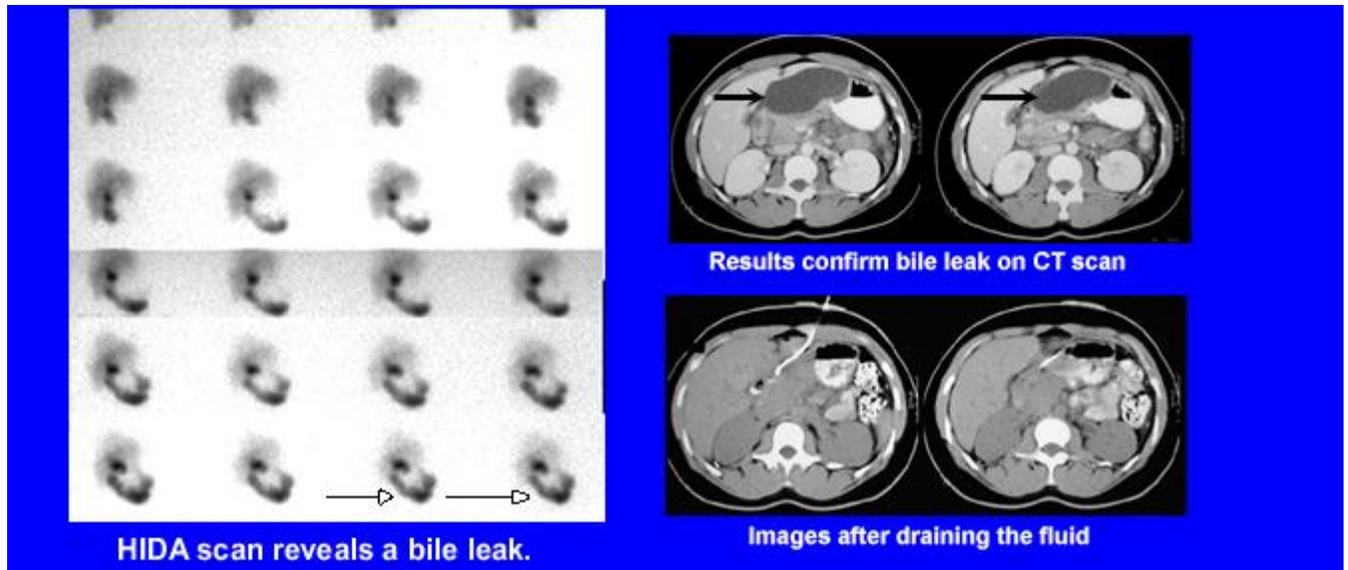
- a) Urticaria and rash have been rarely reported with the use of Technetium Tc 99m Mebrofenin since market introduction. Rare cases of chills and nausea have been reported with related compounds.

17. TYPICAL HEPATOBILIARY SCANS IN VARIOUS DISEASES

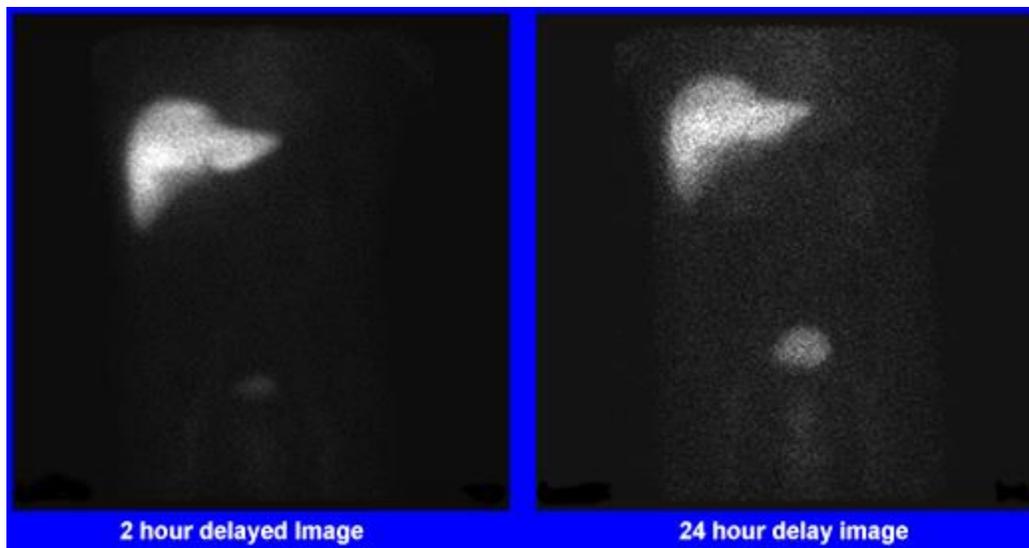
- a) Hepatobiliary scan demonstrating an obstructive pattern after 1 h of imaging time with lack of visualization of intrahepatic and extrahepatic bile systems, gallbladder and small intestinal activity, Reference: **World J Nucl Med. 2013 May-Aug; 12(2): 54–56.**



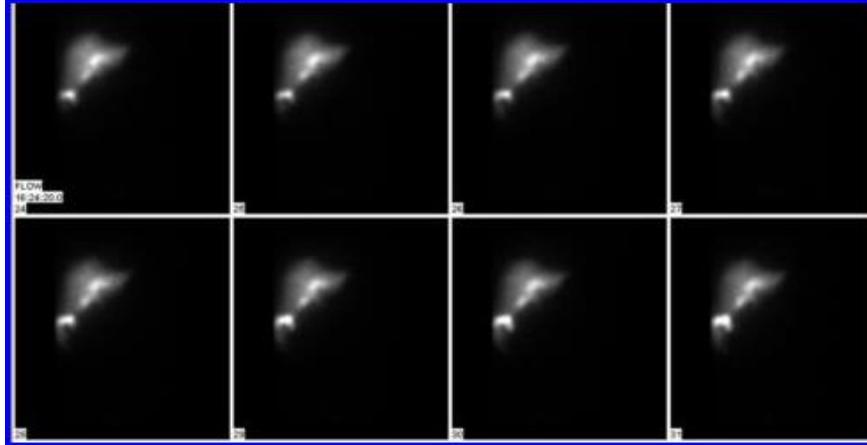
- b) This is an example of a bile leak, which occurred after surgery, caused when this patient underwent laparoscopic cholecystectomy. Two weeks after surgery the patient was examined in the ER and complained of vomiting, low grade fever, and tenderness in the URQ of the abdomen



- c) Patient has URQ pain. No bile flow is seen on the two or twenty-four-hour images. Shortly after this exam, LFTs and bilirubin became elevated and ERCP was performed. Sludge and stones were cleared from the bile ducts during ERCP and the patient experienced symptomatic relief, as well as a decrease in LFTs and bilirubin. The cause of the HIDA scan appearance as depicted above was high-grade biliary obstruction. Shortly after this exam, LFTs and bilirubin became elevated and ERCP was performed.



- d) Patient underwent laparoscopic cholecystectomy five days prior to this study. She was admitted to the ER with belly pain and vomiting. The following hepatobiliary scan was taken over 60 minutes. Diagnosis: Biliary leak with pooling within the gall bladder fossa and the right paracolic gutter.



18. INTERNAL RADIATION DOSIMETRY

RADIATION DOSIMETRY

The estimated absorbed radiation doses ¹⁻² to organs and tissues of an average subject (70 kg) from an intravenous injection of 370 MBq (10 millicuries) of Technetium Tc 99m Mebrofenin are shown in Table 4.

TABLE 4

Estimated Absorbed Radiation Doses[†]

Tissue	Normal Subjects*		Severely Jaundiced Patients**	
	mGy/ 370 MBq	rads/ 10 mCi	mGy/ 370	rads/ 10mCi
Total Body	2.0	0.2	1.7	0.17
Liver	4.7	0.47	8.1	0.81
Gallbladder Wall	13.7	1.37	12.5	1.25
Small Intestine	29.9	2.99	16.0	1.60
Upper Large Intestine Wall	47.4	4.74	24.8	2.48
Lower Large Intestine Wall	36.4	3.64	19.7	1.97
Kidney	2.2	0.22	1.9	0.19
Urinary Bladder Wall	2.9	0.29	24.2	2.42
Ovaries	10.1	1.01	6.4	0.64
Testes	0.5	0.05	1.1	0.11
Red Marrow	3.4	0.34	2.5	0.25

[†]Method of Calculation:

(1) Loberg, M.D., Buddemeyer, E.V.: Application of pharmacokinetic modeling to the radiation dosimetry of hepatobiliary agents. In Third International Radiopharmaceutical Dosimetry Symposium, FDA No. 81-8166, U.S. Department of Health and Human Services, Public Health Service, FDA, Bureau of Radiological Health, Rockville, MD, (1981) pp. 318-332.

(2) Values for S: "S", Absorbed Dose per Unit Cumulated Activity for Selected Radionuclides and Organs, MIRD Pamphlet No. 11 (1975).