

# The non-conventional use of $^{99m}\text{Tc}$ -Tetrofosmine for dynamic hepatobiliary scintigraphy

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## Abstract

**BACKGROUND:** Classic dynamic hepatobiliary scintigraphy (DHBS) is commonly performed with  $^{99m}\text{Tc}$ -Iminodiacetic Acid (IDA) derivatives and represents a non-invasive diagnosis method for biliary dyskinesia, fistulas, surgical anastomosis, etc (1). This study assesses the possibility of performing DHBS with  $^{99m}\text{Tc}$ -Tetrofosmine (TF), a radiopharmaceutical (RF) dedicated to myocardial perfusion scintigraphy (MPS), but being excreted through the liver. The possibility to use  $^{99m}\text{Tc}$ -TF for DHBS may be important in situations when the standardized RF for this procedure (IDA derivatives) is not available.

**MATERIAL AND METHODS:** We performed DHBS for 30 patients referred for investigation by internal medicine and surgery departments. The patients had been fasting for 12 hours. The dynamic investigation started simultaneously with the intravenous (IV) administration of 37–110 MBq (1–3 mCi)  $^{99m}\text{Tc}$ -TF. Dynamic images were recorded for 30–45 minutes, one image per minute, followed by static scintigraphy at 1 h, 1.5 h, 2 h, and 3 h after IV injection.

**RESULTS:** The quality of scintigraphic images of the liver and biliary tree obtained at DHBS with  $^{99m}\text{Tc}$ -TF ensured the correct diagnosis of biliary dyskinesia, stasis, stenosis, and fistulas.

**CONCLUSIONS:** DHBS using  $^{99m}\text{Tc}$ -TF is justified by the image quality and by the good cost/benefits ratio. Because the IDA derivatives are not always available, this finding may be important for medical practice.  $^{99m}\text{Tc}$ -TF evacuated through the bile duct allows DHBS interpretation, while the necessary dose is approximately 8 to 20 times smaller than that used for myocardial perfusion scintigraphy.

**Key words:** biliary, bile tract, cholescintigraphy, dynamic hepatobiliary scintigraphy, liver, tetrofosmin

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## Introduction

Classically performed DHBS is based on the pharmacokinetics of  $^{99m}\text{Tc}$ -Hydroxy Iminodiacetic Acid (HIDA) and similar derivatives of IDA [1]. After IV administration,  $^{99m}\text{Tc}$ -HIDA is rapidly accumulated in the liver and after a short intrahepatic transit time, the RF is excreted (the same as the molecular complexes with molecular mass higher than 300) through the biliary system into the duodenum [1]. About 85–90% of  $^{99m}\text{Tc}$ -HIDA is eliminated through the liver, the percentage depending on the status of hepatocyte function [2].

Scintigraphic images are recorded for 45–60 min, 1 image for each 2 minutes, the recording starting simultaneously with IV injection of RF [1].

The liver is visualized with  $^{99m}\text{Tc}$ -HIDA in normal cases within 0–5 min after IV injection, the common biliary duct — within 5–20 min, gallbladder — within 10–40 min, duodenum — within 15–45 min, and the kidneys — within 0–5 min [2].

In the past few years, the Romanian market of RF products was limited due to economic reasons and legislative gaps. In this context, IDA derivatives have not been available for DHBS investigations for more than 5 years. This study is a result of our efforts to maximally use the potential of the pharmaceuticals which are still available, in order to perform certain investigations which otherwise would not be possible.

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The visualization of liver and extrahepatic bile ducts using  $^{99m}\text{Tc}$ -TF for MPS has its inconveniences. However, it challenged us to test the possible assessment of the biliary tree using TF.

In our desire to perform DHBS using TF, we also referred to the studies aimed at increasing the quality of MPS by accelerating the biological clearance of  $^{99m}\text{Tc}$ -TF through the hepatic bile tree using a high fat lunch, milk, lemon juice, etc [5–14, 16–18].

Hepatic tumours and impairment of bile drainage were only incidentally reported when performing MPS with TF [11–13, 19, 20].

## Material and methods

### Radiopharmaceutical

TF (Myoview) is a pharmaceutical commonly used for myocardial perfusion studies after radioactive marking with  $^{99m}\text{Tc}$ . Its active substance is sodium TF [6,9-bis(2-ethoxyethyl)-3,12-dioxo-6,9-diphosphatetradecane],  $\text{C}_{18}\text{H}_{40}\text{O}_4\text{P}_2$ , in a concentration of 0.23 mg/bottle [3]. The product is created for IV administration to patients after reconstitution is obtained by adding sodium pertechnetate ( $\text{Na}^{99m}\text{TcO}_4$ ) to the bottle. The radioactive marking of TF results from the oxidation-reduction reaction with sodium pertechnetate in the presence of stannous chloride ( $\text{SnCl}_2 \cdot 2\text{H}_2\text{O}$ ) [3].

TF is captured during the first passage by the myocardium cells, with an extraction rate of about 40%. The tracer remaining in circulation is extracted mostly by the hepatic parenchyma (at the level of hepatocytes) and afterwards it is evacuated it follows the bile tree (being a lipophilic complex with molecular mass 895), with less than 15% being eliminated through the kidneys [3, 4, 22]. In our study the right kidney image has shown to be an inconvenient due to its.

The time of appearance of TF in different parts of the bile tree has not been standardized yet. Because the common bile duct area is usually placed over the right kidney region, recording the dynamic parameters for the common bile duct is of less importance than identification of stasis.

### Patient characteristics

We examined a total of 30 patients aged  $58.4 \pm 11.2$  years, 8 men and 22 women.

Fourteen patients were normal controls aged  $38.5 \pm 9.5$  years, investigated in order to establish the basic aspect of the investigation. Ten of them were referred to our department for MPS without having liver or biliary illness.

### Scintigraphy protocol

The patients were fasted for 12 hours before the examination so as not to influence the biological clearance of  $^{99m}\text{Tc}$ -TF. The cases were referred for investigation by the internal medicine and surgery departments of our hospital. We were not involved in the selection.

The investigations were performed with a SPECT Orbiter Siemens gamma-camera equipped with a low-energy, high-resolution, parallel collimator. The acquisition and processing of data were performed using a Power Macintosh computer connected to the gamma-camera, using the ICON programs designed for scintigraphy investigations.

In order to perform DHBS, we respected the preparation procedure of  $^{99m}\text{Tc}$ -TF as indicated in the product's prospectus. The

RF administration to patients was done via IV injection in doses of 37–110 MBq (1–3 mCi), depending on the patient's weight.

The dynamic scintigraphy images were acquired during 30–45 min, starting at the moment of RT IV injection, one image per minute, in the anterior view. We decreased the time for each image as compared to DHBS with HIDA (1 image/min) instead of 1 image/2 min, in order to obtain a better sensitivity. The patients were placed in the supine position since the investigation involved the hepatic and intestinal areas. Static scintigraphy images of the abdomen area were acquired at 1 h, 1.5 h, 2 h, and 3 h post-injection, after the dynamic acquisition of data.

All scintigraphic investigations presented in this study were performed at the Nuclear Medicine Laboratory of the Clinical Emergency Hospital "Prof. Dr. O. Fodor" Cluj-Napoca, by the same team.

The radioactive marking of the pharmaceutical product, acquisition of data, and compliance of radiological security conditions were performed by the laboratory's physicist. The interpretation of images was made by our department's medical doctor.

### Radiation dosimetry

In order to introduce into use a new investigation based on a radiopharmaceutical already approved for another type of scintigraphy, it is absolutely necessary to respect the radioprotection of patients and medical personal according to ALARA (As Low As Reasonably Achievable) principles.

Because  $^{99m}\text{Tc}$ -TF is a radiotracer widely used for MPS, its dosimetry is standardized for the higher doses used in MPS [3]. The gallbladder walls absorb the highest doses, followed by the intestine [3].

Because the doses which we used at DHBS were 8–20 times smaller than at MPS, internal irradiation is also lower than during MPS, which had already been shown as respecting ALARA principles. This fact justifies the use of TF for DHBS in a radioprotection point of view, in addition to the favourable ratio between irradiation and diagnosis benefit.

## Results

Comparing the scintigraphy images at DHBS using  $^{99m}\text{Tc}$ -TF with those which we have in our laboratory database, obtained with  $^{99m}\text{Tc}$ -HIDA, we have been able to show that the resolution of scintigraphic images with  $^{99m}\text{Tc}$ -TF allows the visualization of intrahepatic and extrahepatic bile tree. After the injection of 37 MBq  $^{99m}\text{Tc}$ -TF the bile ducts of the left and right lobes, biliary confluent, common bile duct, and gallbladder can be visualized accurately. The stasis is easy to detect both the intrahepatic and extrahepatic bile tree.

The quantity of RF eliminated through the liver is enough to allow an increase in the region of interest of dynamic curves having low amplitude fluctuations.

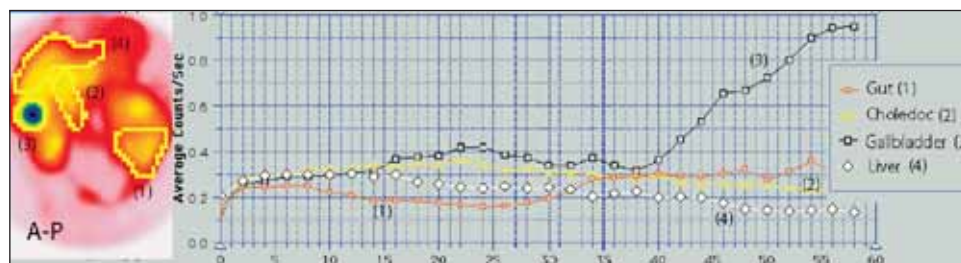
Visualization of the myocardial area is not an impediment in interpretation of DHBS with  $^{99m}\text{Tc}$ -TF and does not impose higher doses than at DHBS with  $^{99m}\text{Tc}$ -HIDA.

### Normal aspect

In normal patients, maximum amplitude of liver curve occurred at  $10 \pm 5$  min. The half-time of the liver curve amplitude (calculated

**Table I. Pathologic cases**

Referral diagnosis	No patients	Females	Males	Normal aspect on scintigraphy	Pathologic scintigraphic results
Biliary dyskinesia	12	10	2	2	10
Post-anastomotic fistula	1	1	–	–	1
Lack of colloidal tracer on liver scintigraphy in biliary confluent area	1	1	–	–	1
Common bile duct stenosis	1	1	–	–	1

**Figure 1.** Biliary dyskinesia with lack of gallbladder drainage and bile stasis in the common bile duct.

on extrapolated histogram) was at  $60 \pm 12$  min after injection. The left lobe biliary duct was visualized at  $21 \pm 4$  min. The right lobe biliary duct is commonly difficult to see because of gallbladder and right kidney superposition.

In 8 normal cases (without clinical dyskinesia symptoms), the duodenum was not visualized at 45 min and 1 h after the injection.

The gallbladder was visualized starting with  $28 \pm 7$  min after the injection.

### Pathological aspects

Table I presents the pathological cases. For two patients with clinic biliary dyskinesia, DHBS showed normal aspect.

The other 14 patients referred to us for DHBS had abnormal dynamic findings.

Ten patients with clinical diagnosis of biliary dyskinesia had the following particularities:

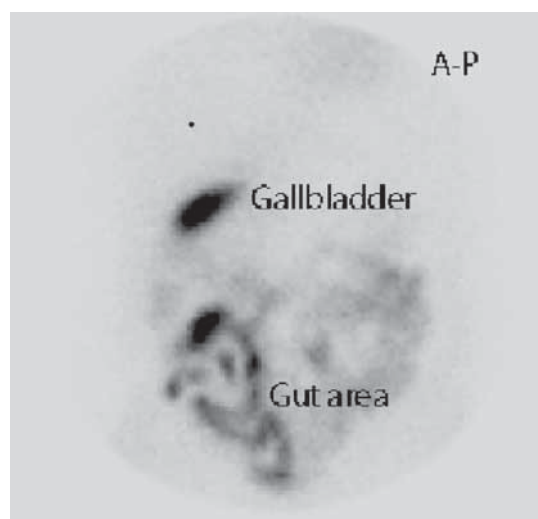
- in 6 cases the gallbladder was not visualized during the dynamic investigation and on 1h post-injection static image. For 2 of these, the gallbladder also did not appear on static images recorded at 1.5 h, 2 h, and 3 h, while for 4 of them the gall bladder could only be visualized on static images at 2 h and 3 h (Figures 1, 2). Clinical diagnosis of acute cholecystitis was excluded for those patients.

One patient had important stasis on the biliary confluent area and partly in the left lobe bile duct.

For two patients the tracer arrived to the gallbladder in due time, but its excretion in the duodenum at 45 minutes and 1 h post-injection was very small, although no stasis or obstacle was found

One patient had an incomplete obstacle at the level of the junction of the cystic duct with the common biliary duct. ERCP confirmed this diagnosis (Figure 3).

We also investigated two post-surgery patients suspected of having fistulas: one of them with bilio-intestinal fistula (Figure 4) and the other with bilio-bronchial fistula. For the both of them,

**Figure 2.** Biliary dyskinesia — static images at 3 hours after injection with remnant tracer in the gallbladder.

DHBS highlighted RF stasis at the origin point of the fistula and pathological dynamic of RF determined by the fistula. The thin trajectory of fistulas could not be visualized.

Another case was of a 52-year-old woman who had a defective uptake of tracer in the hilum area liver scintigraphy with radio-colloid. DHBS detected a dilation of intrahepatic biliary tree with important stasis in the biliary confluent area (Figure 5).

For a patient diagnosed clinically with common bile duct obstructed by a bile stone, DHBS showed a dilated common bile duct, most probably due to an incomplete obstacle at the level of the Oddi sphincter. This diagnosis was confirmed by ERCP.

The dynamic liver aspect for an asymptomatic patient is shown in Figure 6. The liver curve reaches its highest amplitude at 10 min post-injection. Half of the liver curve amplitude calculated

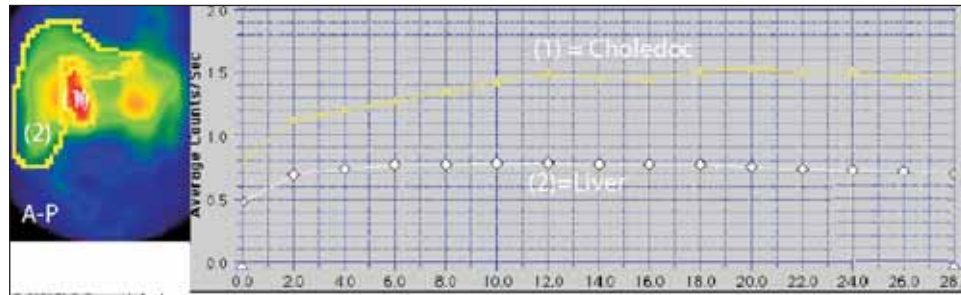


Figure 3. Stasis in the common bile duct.

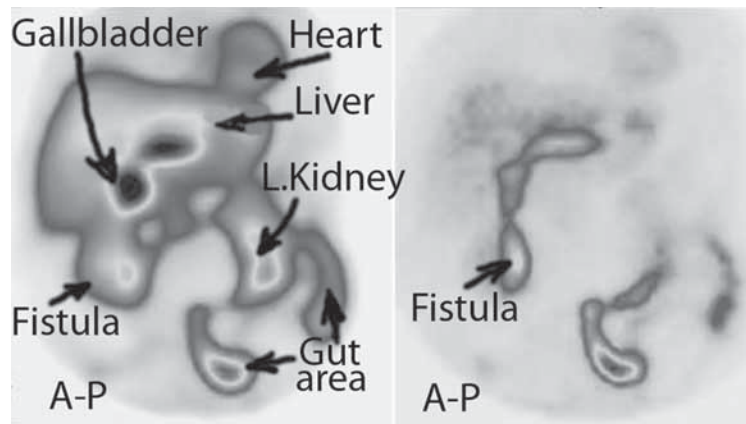


Figure 4. Bilio-intestinal fistula — static images at 1 hour and 2 hours after injection.

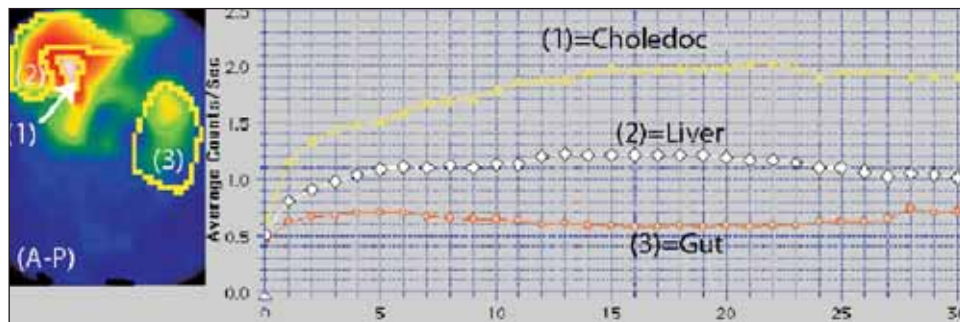


Figure 5. Transient stasis in the common bile duct with delayed tracer drainage in the gut.

by extrapolation is at 50 minutes post-injection (half-time of the liver = 40 min). There was no tracer in the gut area at 45 min after injection. The tracer arrived at the gallbladder at 28 min post-injection, without emptying at 45 min post-injection (gallbladder curve is not presented in the image due to its considerably higher amplitude than that of the liver).

## Discussion

DHBS with  $^{99m}\text{Tc}$ -HIDA was performed in our laboratory until 2005. Since then, HIDA and other IDA derivatives have been no longer available on the Romanian RF market. Consequently, we were not able to answer requests for DHBS, leaving us compelled to find a solution to be able to again perform such investigations.

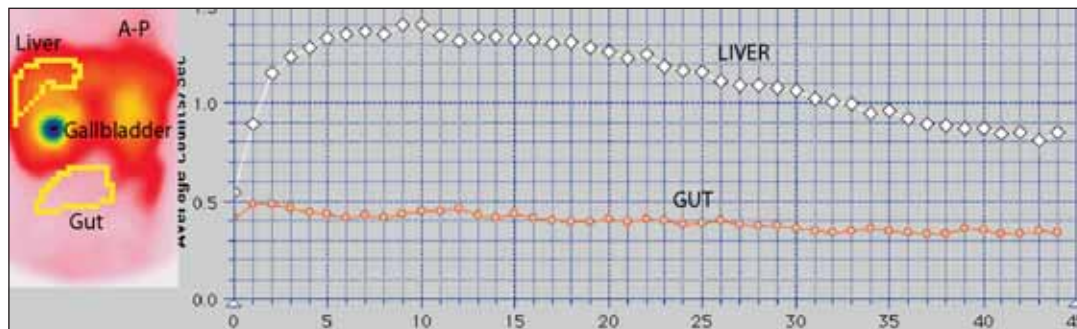
Use of TF as RF for DHBS has been based on its pharmacokinetics involving excretion through the liver and biliary tree.

After introducing  $^{99m}\text{Tc}$ -TF in the practice of our laboratory (for MPS and parathyroid scintigraphy) we have been able to verify the good resolution of images of the liver and biliary tree area during these standard investigations.

The bibliography includes several studies related to the opportunity to influence the time of evacuation from the liver of  $^{99m}\text{Tc}$ -TF at MPS using different types of foods [5–11, 16–18].

We found information about several cases of liver or biliary pathology incidentally reported at MPS [11–13, 19, 20]. Some later studies used TF to determine ejection fraction of the gallbladders of patients referred for MPS [21].





**Figure 6.** Dynamic hepato-biliary scintigraphy for an asymptomatic woman, 35-years-old.

Because the tracer  $^{99m}\text{Tc}$ -TF is the first-choice for MPS and it is currently used for this investigation, performing DHBS by using residual tracer from MPS has great advantages in an economical point of view.

Due to the fact that the RF used does not contain iodine, DHBS with  $^{99m}\text{Tc}$ -TF may be performed in allergic patients in whom iodine-based radiological contrast agents cannot be used.

From a radioprotection point of view, use of TF for DHBS respects irradiation limits.

We were therefore able to be of help with scintigraphy diagnosis for various dyskinesia cases, biliary fistulas, biliary stasis, and common bile duct stenosis.

## Conclusions

Biliary drainage of  $^{99m}\text{Tc}$ -TF allows the acquisition of good quality images of the intra-hepatic bile tree, common bile duct, and gallbladder. The good resolution of images allows identification of intra- and extrahepatic stasis areas, as well as the dynamics of tracer at their level.

The tracer quantity evacuated in the bile tree is enough to allow rising dynamic curves with good resolution. The dynamics of  $^{99m}\text{Tc}$ -TF allows late visualization of bile tracts, up to 3 hours after the injection.

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## Conflict of interest

None to declare.

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