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# $^{99m}$Tc-IOTIDA (3-iodo 2,4,6-trimethylpheyl carbamoylmethyl iminodiacetic acid) for Cholescintigraphy

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## *ABSTRACT*

Various $^{99m}$Tc-IDA derivatives are used clinically for the assessment of the hepatocytic function, the functional status the cystic duct and gallbladder. In this study, $^{99m}$Tc-IOTIDA was prepared and evaluated its *in vivo* pharmacokinetic behaviour through animal studies. The radioilabeling efficiency of $^{99m}$Tc-IOTIDA was maintained with high radiochemical purity (> 95 %) at room temperature for 6 hours. The serial static image scans of rabbit administered with $^{99m}$Tc-IOTIDA revealed that none of the tissues except the hepatobiliary system has radioactivity concentrations. Biodistribution of $^{99m}$Tc-IOTIDA in rats showed that 90 % of the injected dose was excreted via the pathway of the liver. The scintigraphic views for a healthy volunteer revealed that the most of the administrated radioactivity is accumulated in the liver.

Further evaluations for $^{99m}$Tc-IOTIDA including the resistance to the competitive effects against bilirubin and sophisticated chemical studies for kit formulation are needed. In conclusion, $^{99m}$Tc-IOTIDA can be used as a potential hepatobiliary imaging agent for the evaluation of the functional status of the hepatocytes and the patency of the biliary duct.

**KEY WORDS**. Cholescintigraphy, Hepatobiliary imaging, $^{99m}$Tc-IOTIDA

## 1. Introduction

The radiopharmaceuticals used for liver imaging are divided into two categories based on the physiologic function of the liver they are designed to evaluate.

One is used to evaluate the functional status of the hepatocytes and the patency of the biliary duct, and the other the phagocytic function of the Kupffer cells. The typical ones of the former are the lipophilic compounds labeled with raionuclides and the radiolabeled colloids are the latter. Two different classes of $^{99m}$Tc complexes for hepatobiliary studies having been approved for human use are iminodiacetic acid and pyridoxalamino acid derivatives [15].

All of the $^{99m}$Tc radiopahrmaceuticals for hepatobiliary imaging show similar pharmacokinetic properties in animals and human. They are effectively extracted from the blood by the liver and excreted into bile. Furthermore, they assess disease that the hepatocytic function, the functional status the cystic duct and gall bladder. That is, biliary duct patency and hepatic diseases can be assessed by the scintigraphic procedure called cholescintigraphy.

The most of the hephatobiliary agents labeled with $^{99m}$Tc are the class of iminodiacetic acid derivatives including $^{99m}$Tc-disofenin (2,6 diisopropylpheyl carbamoylmethyl iminodiacetic acid, DISIDA) [13], $^{99m}$Tc-mebrofenin (3-bromo 2,4,6 trimethylpheyl carbamoylmethyl iminodiacetic acid) [2, 3, 4, 6, 10], $^{99m}$Tc-EHIDA (2,6 diethylpheyl carbamoylmethyl iminodiacetic acid) [13] $^{99m}$Tc-lidofenin (2,6 dimethylpheyl carbamoylmethyl iminodiacetic acid) [1, 7] and $^{99m}$Tc- JODIDA (3 iodo 2,4 diethylpheyl carbamoylmethyl iminodiacetic acid) [3].

The structural and physicochemical relationships between lipophilic and polar groups on the radiolabeled complexes play a key role in the determination of the binding affinity of the radiopharmaceuticals to hepatic transport proteins, the efficiency of their hepatocyte uptake, the excretion rate.

In general, the increase of lipophilicity by attaching more alkyl chains and lengthening the alkyl chain on the benzene ring of the IDA molecule shows more hepatic uptake and less renal excretion [5].

The liver activity can be seen within a few minutes after injection, but it cleared quickly and appears in the gallbladder and then in the intestine. As hephatocellular function decreases and the bilirubin level progressively upsurges, the renal excretion of the complex increases.

Among the IDA derivatives, $^{99m}$Tc-mebrofenin combines the best characteristics of high hepatic uptake, low urinary excretion, fast blood clearance and hepatocellular transit.

The uptake and excretion parameters of three $^{99m}$Tc-IDA derivatives, $^{99m}$Tc-EHIDA, $^{99m}$Tc-DISIDA, $^{99m}$Tc-mebrofenin was summarized at **Table 1** [11].

$^{99m}$Tc-disofenin and $^{99m}$Tc-mebrofenin are the best agents for hepatobiliary imaging in that they provide good images when the bilirubin level is 20 to 30 mg/100 ml. Furthermore, $^{99m}$Tc-mebrofenin has much less renal clearance and the highest degree of resistance to the competitive effects of bilirubin.

The ideal conditions of the $^{99m}$Tc hepatobiliary agents are described as follows;

1) high hepatocytic uptake and fast hepatic clearance with less renal excretion
2) better ability to compete against bilirubin for binding to cellular transport proteins nevertheless with high bilirubin level

3) easy preparation and high radiochemical purity

As for $^{99m}$Tc-Mebrofenin, substitution of three methyl groups at the *ortho* and *para* positions and bromine at the *meta* position increases the hepatic extraction, decreases hepatocellular transit time, and impacts a high degree of resistance to the competitive effects of bilirubin and low urinary excretion [10].

However, the substitution of ethyl or *iso*-propyl group on the *ortho* position of the phenyl ring of IDA derivatives decrease lipophilicity and protein binding.

As compared to $^{99m}$Tc-EHIDA, substitution of iodine on the *meta* position of the phenyl ring of EHIDA increases the hepatic extraction as well as in comparison of $^{99m}$Tc-disofenin, the $^{99m}$Tc complex gives better visualization of the biliary system when the bilirubin level is high [13].

In this study, we synthesized 3-iodo 2,4,6 -trimethylpheyl carbamoylmethyl iminodiacetic acid (IOTIDA) which iodine, instead of bromine, was substituted at the *meta* position of the phenyl ring, then evaluated as a hepatobiliary agent using animals.

Furthermore, serial scans of a healthy volunteer after intravenous administration of $^{99m}$Tc-IOTIDA were obtained.

## Materials and Methods

2,4,6-trimethylaniline (97 %), iminodiacetic acid disodium salt monohydrate (97 %), and chloroacetylchloride (98 %) was purchased from Aldrich Chemical Co. (Milwaukee, USA). Iodine ($I_2$) was purchased from Merck KGaA (Damstadt, Germany).

All other chemicals used in this study were of AR grade.

Sodium pertechnetate ($Na^{99m}TcO_4$) was obtained from a $^{99}$Mo-$^{99m}$Tc generator (Daichi, Japan). The radiolabeling yield was determined by an ITLC scanner (EG & G Berthold linear Analyzer). The radioactivity was measured using an ionizing chamber (Capintec 15R, BIODEX Atomlab 200).

The thin layer chromatography (TLC) pattern of $^{99m}$Tc-IDA complex on silica alumina impregnated glass fiber sheets using 20 % aqueous NaCl solution as a developing solvent showed that $^{99m}$Tc-IDA complex and $^{99m}TcO_4^-$ was found at origin (0.0 ~0.2) and at solvent front (0.9 ~ 1.0), respectively. In case where water was used, $^{99m}$Tc-IDAs and $^{99m}TcO_4^-$ was confirmed at solvent front, in contrast, $^{99m}TcO_2$ (colloid) at origin. The labeling efficiency was calculated as follows; Labeling efficiency (%) = 100 – [% of $^{99m}TcO_4^-$] – [% of $^{99m}TcO_2$]

For the nuclear imaging study, lyophilized vial kits of IOTIDA was used.

**Synthesis of 3-iodo-2,4,6-trimethylphenyl carbamoylmethyl-iminodiacetic acid (IOTIDA)**

3-iodo-2,4,6-trimethylphenyl carbamoylmethyl-iminodiacetic acid (IOTIDA) was prepared by the reported method with minor modification as given in **Scheme 1** [8, 12].

Melting point were determined using Fischer Johns melting point apparatus

**2,4,6-trimethylphenyl carbamoylmethyl chloride (1)**

A solution of 2,4,6-trimethyl aniline (13.52 g, 100 mmol) in glacial acetic acid (100 ml) was placed in ice bath to maintain the temperature at below 5 °C and chloroacetylchloride was added dropwise under nitrogen atmosphere in order to keep the evaluation of hydrogen chloride under control. Upon completing the addition, it was allowed to stand at room temperature for 1 hr. Sodium acetate (19.7 g, 240 mmol) in water (100 ml) was added in portion and was allowed to stand for additional 1 hr.

The precipitate was filtered and was then dried in *vacco* and recrystallized from ethanol to give 85 % yield of the title compound (21.1 g): mp 177 ~ 178 °C;

**3-iodo-2,4,6-trimethylphenyl carbamoylmethyl chloride (2)**

To a solution of (Ⅰ) (21 g, 100 mmol) in a mixture of glacial acetic acid (150 ml), water (10 ml) and concentrated $H_2SO_4$ (3 ml) were added $KIO_4$ (4.6 g, 40 mmol) and Iodine (20.4 g, 160 mmol) under continuous stirring.

The reaction mixture was heated to 100 °C for 1 hr and was allowed to stand for 1 hr at room temperature. The excess of iodine was eliminated by the addition of sodium sulfite anhydrous (1.5 g) in water (300 ml). The precipitate was filtered, washed with water and dried in *vacco*.

It was recrystallized from absolute ethanol to give 72 % yield of the title compound (24.1 g) : mp 180 ~ 182 °C;

**3-iodo-2,4,6-trimethylphenyl carbamoylmethyl-iminodiacetic acid (IOTIDA) (3)**

A solution of iminodiacetic acid disodium salt monohydrate (10.04 g, 50 mmol) in water (100 ml) was added to a solution of (Ⅱ) (16.68 g, 50 mmol) in ethanol (200 ml) and then the reaction mixture was heated to reflux for 8 hrs. During the reaction, the reaction mixture was maintained an alkaline medium (pH 11) by the dropwise addition of NaOH. At the point when the change of pH was not occurred, the reflux was stopped and allowed to stand overnight at room temperature. After elimination of ethanol, the remaining mixture was extracted with diethyl ether (2 x 50 ml) which was discarded. The aqueous phase was adjusted at pH 2.5 with the dropwise addition of conc. HCl.

The precipitate was filtered and washed with diluted HCl and dried in *vacco*. Recrystallization from absolute ethanol gave 64.5 % of the title compound (14 g): mp 213 ~ 214 °C;

**Preparation of $^{99m}$Tc-IOTIDA**

In-house prepared lyophilized vial of IOTIDA was used which contains 40 mg of IDA derivative, 0.4 mg of $SnCl_2$ for each vial. During the preparation of the lyophilized vials, it was adjusted at pH 5.8 ~ 6.0.

$^{99m}$Tc-complexes were prepared by mixing of lyophilized compound and stannous(II) chloride with generator eluted $Na^{99m}TcO_4$ in saline (1 ml, 370 MBq) at room temperature for 10 mins in order to perform the chelation with IDA derivative molecules.

In these experiments, labeling efficiency of $^{99m}$Tc- IOTIDA was determined by performing ITLC on silica gel impregnated glass fiber sheets using 20 % aqueous NaCl solution and water as developing solvents.

**Animal Experiments**

To examine the *in-vivo* retention of $^{99m}$Tc- IOTIDA, male Sprague-Dawley rats (6 week-old) and male New Zealand white rabbits (6 week-old) were used. The animals were kept in individual cages at 22 ± 1 °C with a relative humidity of 60 ± 10 % and a 12 hr light/dark cycle. The animals were allowed free access to food and water, and were used after acclimation for 1 week.

$^{99m}$Tc- IOTIDA was administered intravenously to the rats via tail vein for biodistribution studies and to the rabbits via an ear vein for imaging tests such as dynamic kinetics and serial image scans using a gamma camera (Orbiter, Simens, USA).

**Nuclear imaging**

Six week-old New Zealand white male rabbits (2.5  3.0 kg) were used for imaging studies, which were anesthetized with ketamine and xylazine. A $^{99m}$Tc-IDA complex was injected, respectively, to a rabbit via the left ear vein with 37 MBq/0.5 ml. All of the rabbits were placed in a posterior position. To confirm the dynamic kinetics of $^{99m}$Tc-IOTIDA, whole-body dynamic images for 30 min were obtained using a gamma camera fitted with a low energy all-purpose collimator. A 20 % window was centered around 81 keV.

Image data were analyzed under the dynamic procedure of the SCINTRON IV system (Medical imaging electronics, Germany).

**Biodistribution Studies**

$^{99m}$Tc-IOTIDA, with 7.4 ± 0.7 MBq/ 0.2 ml (0.2 ± 0.02 mCi) was injected into Sprague-Dawley male rats (SPF grade, 163.8 ± 8.5 g, n=12) through a lateral tail vein.

To determine the radioactive concentration in the tissues and organs, the animals were sacrificed after being anesthetized at 10, 30 and 120 mins after administration (4 animals per each group). Tissues and

organs were excised and weighed. The radioactivity in the samples was counted for 1 min using a gamma well counter (Canberra, USA). The measured counts were corrected along with the same radioactivity of a standard injected radiopharmaceutical.

The distribution in each organ was calculated from the above data and expressed as percent injected dose per gram tissue (%ID/g).

**Human Study**

Serial images were acquired after administration of $^{99m}$Tc-IOTIDA (185 MBq) to a healthy male volunteer (55 year-old) with a scintillation camera at the given time intervals 5, 10, 15, 20, 25, 30, 45 and 60 mins. The volunteer fasted for 12 hr before administration.

The serial images were acquired by the assistance of medical staff of the Asan Medical Center in Seoul.

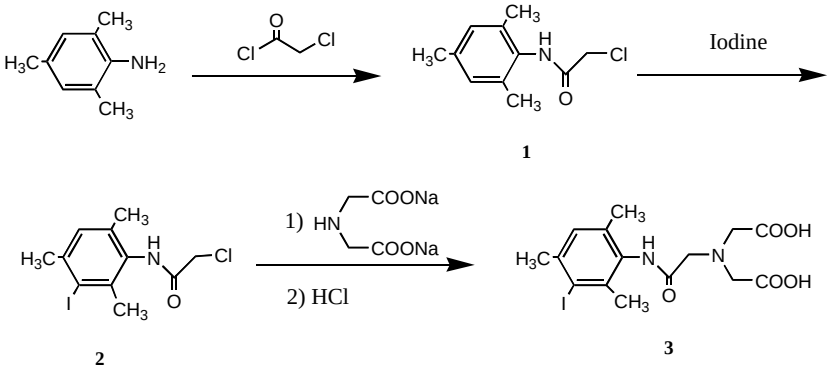
# Results

**Synthesis of 3-iodo-2,4,6-trimethylphenyl carbamoylmethyl-iminodiacetic acid (IOTIDA)**

The synthesis procedure starting from 2,4,6-trimethyl aniline makes it possible to give overall yield of 42.4 % of the title compound (14 g), 3-iodo-2,4,6-trimethylphenyl carbamoylmethyl-iminodiacetic acid (IOTIDA).

The IR and $^{1}$H, $^{13}$C spectral data of **3** support the structure of 3 as given in **Scheme 1**.

**Scheme 1.**




**Preparation of $^{99m}$Tc- IOTIDA**

[$^{99m}$Tc]pertechnetate was reacted with IOTIDA in the presence of stannous(II) chloride resulting to the formation of $\{^{99m}Tc(III)[\ IOTIDA]_2\}^{1-}$ **4** as given in **Scheme 2**.

**Scheme 2.**

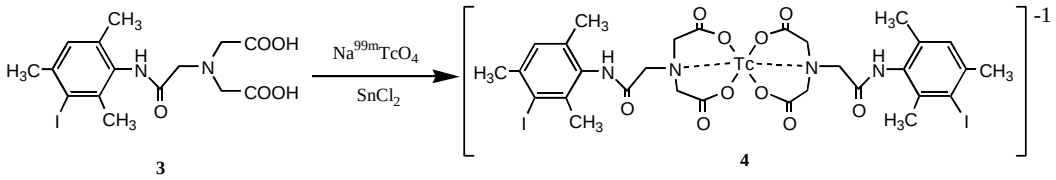



**Table 2** showed the results of TLC for **4** by performing ITLC-SG using 20 % aqueous NaCl solution and water as developing solvents.

The radioilabeling efficiency of $^{99m}$Tc-IOTIDA was maintained with high radiochemical purity (> 95 %) at room temperature for 6 hours.

The typical chromatography graphs on $^{99m}$Tc-IOTIDA are shown in **Fig. 1**.

## Animal Experiments

### Nuclear Imaging

Upon injection, $^{99m}$Tc-IOTIDA are quickly cleared from the blood by the hepatocytes and excreted into the gallbladder and intestine with negligible uptake by the kidneys and other organs.

The serial static image scans of rabbit administered with $^{99m}$Tc-IOTIDA revealed that none of the tissues except the hepatobiliary system has radioactivity concentrations.

The whole-body images of rabbit for 30 mins after intravenously administration of $^{99m}$Tc-IOTIDA was described in **Fig. 2**.

### Biodistribution Studies

92 % of injected dose of $^{99m}$Tc-mebrofenin was transported to the hepatocytes and cleared into gallbladder and intestine with minimal uptake by the other organs. In case where $^{99m}$Tc-IOTIDA was administrated to the tail vein of rats, 90 % of the injected dose was excreted via the pathway of the liver.

The results of biodistribution studies of $^{99m}$Tc-IOTIDA in rats, which are administrated intravenously and scarified at 10, 30 and 120 mins, are summarized in **Fig. 5**, as the percent of injected dose to each selected organ of SD rat (%ID/g). Fast clearance of the $^{99m}$Tc-IDA complex from the blood, liver, and lung was observed within 10 min post injection.

### Human Study

As shown in **Fig. 6**, $^{99m}$Tc-IOTIDA was accumulated in the liver and the gallbladder is visibly in 15 min because the accumulated activity was cleared rapidly from the liver.

The scintigraphic view at 30 min after administration showed that the radioactivity in the liver except

gallbladder was approached to the background level.

## Discussion and Conclusion

The IDA compound reacts with $^{99m}$Tc with the ligand to metal ratio of 2:1 and the complex has -1charge. The $^{99m}$Tc-IDA complex provided a single technetium complex in the +3 oxidation state and demonstrated rapid hepatic clearance after intravenous administration [15].

In an extensive systemic study, the substitution of methyl group on the *ortho* and *para* position and bromine on the *meta* position of phenyl ring of IDA derivatives, Mebrofenin, showed much improved hepatic characteristics [4, 6, 14].

As confirmed from the previous researches for mebrofenin and JODIDA, the substitution of a halogen at the meta position increases hepatic extraction.

In this study, we prepared 3-iodo 2,4,6-trimethylpheyl carbamoylmethyl iminodiacetic acid which the iodine molecule was attached on the *meta* position of the phenyl ring instead of the substitution of bromine.

Considering the outcome of the biodistribution studies using rats, the uptake rate of $^{99m}$Tc-IOTIDA on the other organs, such as kidney, blood is somewhat higher than that of $^{99m}$Tc-mebrofenin as well as hepatocellular transit time is slightly prolonged.

Presumably, those are caused by the pH effect on the complexation of $^{99m}$Tc-IOTIDA. That is, the pH of the lyophilized kit vial can have considerable impact on complex formation.

For the constitution of the lyophilized kit of mebrofenin (Choletec®), the final pH of the kit was adjusted at 5 by the utilization of solubiliser, a mixture of methyl and propylparaben [9].

In general, the IDA derivatives were dissolved at around pH 5.5. Furthermore, the fluctuation of pH in the preparation process of the lyophilized kit makes the degradation of the quality of stannous chloride which provides a bit poor labeling efficiency of $^{99m}$Tc-complex.

In our pre-experiment using DISIDA, as the increase of pH of the kit vial, the excretion through the urinary pathway and plasma protein binding increases. The opposite results were revealed in the case where the pH decreases.

$^{99m}$Tc-IOTIDA was readily excreted through the hepatobiliary system.

The scintigraphic views obtained after intravenous administration of $^{99m}$Tc-IOTIDA to a healthy volunteer revealed that the most of the administrated radioactivity is accumulated in the liver and rapidly excreted through hepatobiliary system to visualize the gallbladder within 15 min. The liver radioactivity outside the gallbladder was approached to the background level with in 30 min.

In conclusion, $^{99m}$Tc-IOTIDA is an alternative as a hepatobiliary imaging agent for the evaluation of the functional status of the hepatocytes and the patency of the biliary duct.

Further evaluations, such as the effects of pH and solubilizer on the kit formulation, are necessary to allow the constitution kit to be used for cholescintigraphy.

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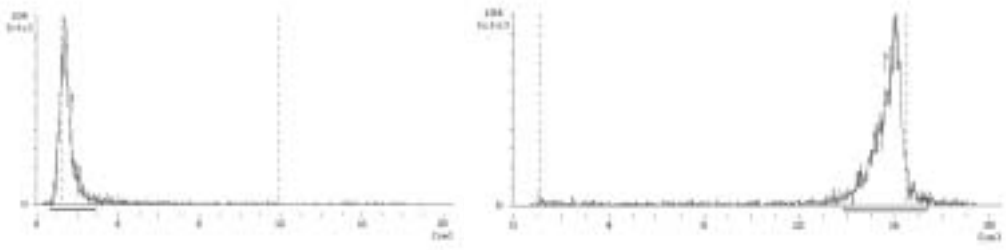
## Table and Figures

**Table 1. Uptake and excretion parameters of $^{99m}$Tc-IDA derivatives**

| $^{99m}$Tc-IDAs | Hepatic uptake(%) | Urinary excretion at 24 h (%) | $t_{1/2}$ of hepatic clearance (min) |
|---|---|---|---|
| $^{99m}$Tc-EHIDA | 82.3 | 17.1 ± 3.2 | 37.3 ± 11.8 |
| $^{99m}$Tc-disofenin | 88.0 | 11.1 ± 1.5 | 19.0 ± 2.5 |
| $^{99m}$Tc-mebrofenin | 98.1 | 1.5 ± 0.3 | 17.0 ± 1.3 |

**Table 2. ITLC analysis of $^{99m}$Tc-IOTIDA**

| ***Chromatographic system*** | | ***$^{99m}$Tc species at*** | |
|---|---|---|---|
| *Support* | *Solvent* | *Origin* | *Solvent front* |
| ITLC-SA | 20 % NaCl | $^{99m}$Tc-IOTIDA, $^{99m}TcO_2$ | $^{99m}TcO_4^-$ |
| ITLC-SA | Water | $^{99m}TcO_2$ | $^{99m}$Tc- IOTIDA, $^{99m}TcO_4^-$ |



(A) (B)

**Fig. 1. The ITLC chromatograms of $^{99m}$Tc-IOTIDA**

**A: ITLC-SA: 20% NaCl; B: ITLC-SA: Water**

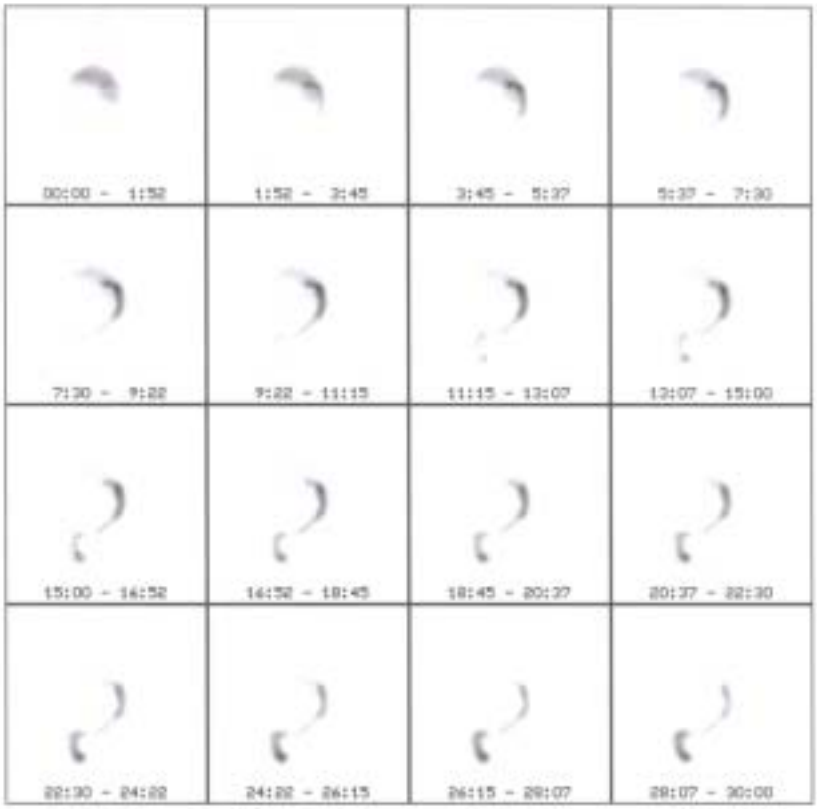



**Fig. 2. The whole-body images of rabbit for 30 mins after intravenously administration of $^{99m}$Tc-IOTIDA.**

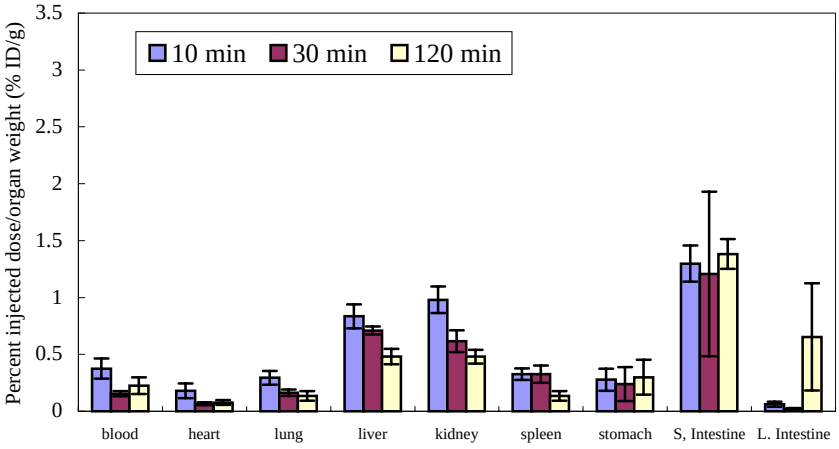



**Fig. 3. Radioactivity concentrations in organs or tissues after intravenous injection of $^{99m}$Tc-IOTIDA in male rats at 10, 30 and 120 mins.**

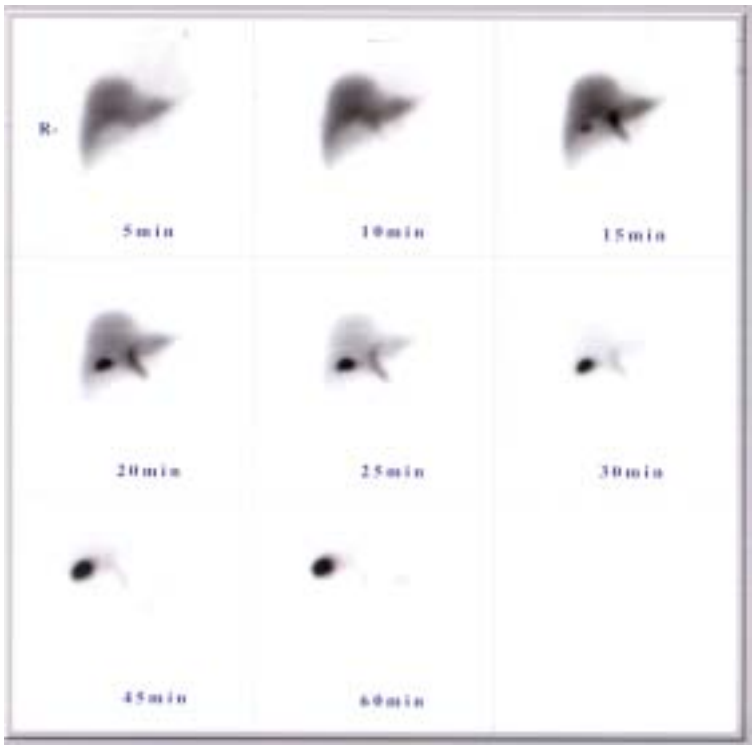



**Fig. 4. The images of healthy volunteer at 5, 10, 15, 20, 25, 30, 45 and 60 mins after intravenously administration of $^{99m}$Tc-IOTIDA.**