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Effect of Ursodeoxycholic Acid on the Biodistribution and Excretion of Technetium-99m Radiopharmaceuticals in Rat: A Potential Image Quality Enhancer

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Purpose: This study aimed to investigate the effect of ursodeoxycholic acid (UDCA) on the biodistribution and excretion of technetium-99m (Tc-99m)-labeled radiopharmaceuticals.

Materials and Methods: Tc-99m hydroxy-methylene-diphosphonate (HDP), Tc-99m pertechnetate, and Tc-99m dimercaptosuccinic acid (DMSA) were injected via the tail vein of rats. After 30 min, the control group was administered saline, and the UDCA group was given UDCA orally. Scintigraphy images were acquired after 30 min and 1, 2, 3, and 4 h. Radioactivity and rate of change were compared. Tc-99m mercaptoacetyltriglycine (MAG_3) imaging was also performed.

Results: In image analysis of Tc-99m HDP, radioactivity of the buttock was lower in the UDCA group at 4 h. Rates of change in the buttock were significantly different at 3 h–30 min and 4 h–30 min, and buttock radioactivity in the UDCA group had decreased more. In analysis of Tc-99m pertechnetate, radioactivity of the buttock was higher in the control group. Rates of change in the thyroid gland and buttock were different at 1 h–30 min, 3 h–30 min, and 4 h–30 min, with radioactivity in the UDCA group decreasing more. In the analysis of Tc-99m DMSA, while the radioactivity of the kidneys in the control group showed little decrease at 1 h–30 min, that in the UDCA group increased. In the analysis of Tc-99m MAG_3 images, radioactivity and radioactivity/total body radioactivity (TBA) values for the kidneys were higher in the UDCA group at 2 min. At 5 and 10 min, radioactivity/TBA values for soft tissue in the UDCA group were lower than those in the control group.

Conclusion: This study demonstrated that administration of UDCA increases renal excretion and soft tissue clearance of radiopharmaceuticals. This investigation could contribute to the broadening of applications of UDCA.

Key Words: Technetium-99m, ursodeoxycholic acid, radioactivity, renal elimination

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INTRODUCTION

Technetium-99m (Tc-99m) scintigraphy is widely used to evaluate the functions of various organs and to diagnose diseases. Among several modalities, Tc-99m diphosphonate bone scintigraphy is most commonly used to survey bone metastasis or to characterize various bone lesions. Tc-99m pertechnetate scintigraphy is widely performed to evaluate thyroid and salivary gland function and to detect ectopic gastric mucosa in Meckel's diverticulum. Tc-99m dimercaptosuccinic acid (DMSA) scintigraphy, which is very sensitive in detecting renal cortical abnormalities, is often used to detect pyelonephritis in patients suspected of urinary tract infection.

Ursodeoxycholic acid (UDCA), the 7-β hydroxy epimer of chenodeoxycholic acid, is normally present in humans at a concentration of about 3% of the bile acid pool and has various hepatoprotective effects that involve increasing the hydrophilicity of bile juice.[1] UDCA modifies the bile acid component by decreasing hydrophobic bile acid levels and increasing nontoxic hydrophilic bile acid levels. It also has a choleretic effect, facilitating hepatocellular bile acid excretion, in addition to exhibiting cytoprotective, membrane stabilizing, and immunomodulatory properties.[2-4] UDCA is also a Food and Drug Administration-approved medicine for cholesterol gall stone dissolution and primary biliary cirrhosis.[5] Although UDCA has been evaluated as an investigational medicine in varying hepatic and extrahepatic disorders, studies applying UDCA to the molecular imaging field are rare.

In a previous clinical study with young, healthy volunteers (mean age: 26.3±2.1 years), hepatobiliary scintigraphy was performed twice per volunteer within 3 days for control and UDCA-treated groups.[6] When the subjects were orally administered a single dose of UDCA (200 mg) 15 min before intravenous injection of Tc-99m diisopropyliminodiacetic acid, the time until visualization of the gallbladder was shortened from 14.2±6.6 to 9.1±2.8 min, and the maximum activity of the gallbladder increased greatly from 83.8±38.4 to 132.3±59.8.[6] With UDCA pretreatment, the gallbladder was clearly visualized at an earlier phase during hepatobiliary scintigraphy. Consequently, UDCA shortened the total imaging time and increased the specificity of hepatobiliary scintigraphy for assessing functional obstruction of the cystic duct.

Furthermore, based on a report that UDCA increases lipase activity, which breaks down triglycerides,[7] we investigated the effects of oral administration of milk and UDCA on the excretion of 2-deoxy-2-[^{18}F]fluoro-d-glucose (F-18 FDG) from various organs of rats.[8] Administration of milk and UDCA enhanced F-18 FDG efflux from the brain, liver, and small intestine. We also noted a significant increase in glucose-6-phosphatase (G6Pase) and a decrease in hexokinase 2 (HK2) expression in organs in the milk+UDCA group, compared to those in the control group.[8] This suggested that F-18 FDG-6-phosphate was dephosphorylated by G6Pase and transformed into F-18 FDG, a chemical structure that easily effluxes from cells. In addition, decreased HK2 expression was also considered to contribute to the back diffusion of F-18 FDG from the organs. Since HK2 phosphorylated F-18 FDG to F-18 FDG-6-phosphate, which is retained in the cytoplasm and hardly diffuses from cells, decreased HK2 expression was thought to increase the portion of F-18 FDG present, compared to F-18 FDG-6-phosphate, resulting in reduced radioactivity in the organs.

As an extension of these previous studies, the current study aimed to investigate the effect of oral administration of UDCA on the biodistribution and excretion of three Tc-99m labeled radiopharmaceuticals, Tc-99m hydroxy-methylene-diphosphonate (HDP), Tc-99m pertechnetate, and Tc-99m DMSA, in rats. Furthermore, we sought to identify possible mechanisms thereof with a Tc-99m mercaptoacetyltriglycine (MAG_3) experiment.

MATERIALS AND METHODS

Animals and materials

Female Sprague-Dawley rats (aged 8–9 weeks old, weighing 190–210 g) were purchased from Orient Bio Inc. (Seongnam, Korea). UDCA (200 mg per tablet) was purchased from Daewoong Pharmaceutical Co. Ltd. (Seoul, Korea). HDP, pertechnetate, DMSA, and MAG_3 were purchased from New Korea Industrial (Seoul, Korea) and labeled with Tc-99m according to the provided procedure. All protocols involving animals were conducted in compliance with the policies and procedures of the Institutional Animal Care and Use Committee of Jeonbuk National University (CBNU 2019-108).

Experimental protocols

Sixty rats were randomly assigned to the control or UDCA group. About 300 μL (74 MBq, 2 mCi) of Tc-99m HDP, Tc-99m pertechnetate, or Tc-99m DMSA was injected via the tail vein of the rats under anesthesia by inhalation of isoflurane (2%). Injection time, dose of the radiotracer prepared, and the dose that remained in the syringe after injection were recorded to calculate the Net injection dose (ID).

Immediately after radiotracer injection, total body radioactivities (TBA) of the rats were measured by placing the rat into a well-type dose calibrator (Capintec Inc., Pittsburgh, PA, USA, 2012). UDCA was prepared by grinding tablets into a fine powder using a mortar and pestle and dissolving the powder in normal saline. Thirty min after radiotracer injection, the control group was administered normal saline (500 μL, 0.9%), and the UDCA group was given 5 mg or 10 mg of UDCA (500 μL) orally using a flexible oral zonde needle (Φ 1.7×90 mm, polyethylene tube, Duksan General Science, Seoul, Korea). The amounts of UDCA were calculated based on the practice guide for dose conversion between animals and humans and previous experiments.[8,9]

At designated time points (30 min and, 1, 2, 3, and 4 h) after

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administration of normal saline or UDCA, images were sequentially acquired for 2 min using a gamma camera (Symbia T16, Siemens Medical Solutions, Malvern, PA, USA, 2011) with an energy peak setting of 140 keV±7.5% for Tc-99m. One detector with a low-energy high-resolution collimator was used at a distance of 7 cm between the detector and the table. During image acquisition, a standard point source of radioactivity about 1.11 MBq (30 μCi) of the same radiopharmaceutical in 1 mL of normal saline was placed at the upper left corner of the image field for image analysis. After all five time points had elapsed, the total body activity of the rat was measured once again using a dose calibrator.

Image analysis

Images were analyzed using PMOD software version 3.7 (PMOD Technologies LLC, Zürich, Switzerland) by drawing a region of interest (ROI) over the relevant organs depending on the type of radiotracer used. For analysis of Tc-99m HDP images, the right shoulder, lumbar spine, liver, and right buttock were chosen. The ROI over the right shoulder was a 10.0×10.0 mm circle, while that over the lumbar spine was an 8.0×16.0 mm rectangle. Those over the liver and right buttock were 12.0×12.0 mm circles (Fig. 1A). For analysis of Tc-99m pertechnetate images, ROIs were drawn over the thyroid gland, stomach, and right buttock. The ROI over the thyroid gland was a 13.0×13.0 mm circle; that over the stomach was a 30.0×25.0 mm oval; and that over the right buttock was a 15.0×15.0 mm circle (Fig. 1B). For analysis of Tc-99m DMSA images, ROIs were drawn over the right kidney, left kidney, and right buttock. The ROI over each kidney was a 22.0×29.0 mm oval, and that over the buttock was a 15.0×15.0 mm circle (Fig. 1C). The ROI over the standard point source was drawn as a 27.2×52.4 mm rectangle in all radiotracer images.

For imaging parameters, radioactivity and rate of change (%) were compared. The first parameter, radioactivity (kBq), was calculated from counts in the ROI using a correction factor deduced from standard point source information. The other parameter, rate of change (%), was calculated as [(radioactivity at each time point–radioactivity of the 30 min image)/radioactivity of the 30 min image] to reflect the rate of change from time 30 min to each specific time point.

Tc-99m MAG_3 experiment

Tc-99m MAG_3 was used to elucidate the mechanism of action of UDCA on radiotracer excretion in the kidneys and from the soft tissues using dynamic image acquisition. Thirteen rats were

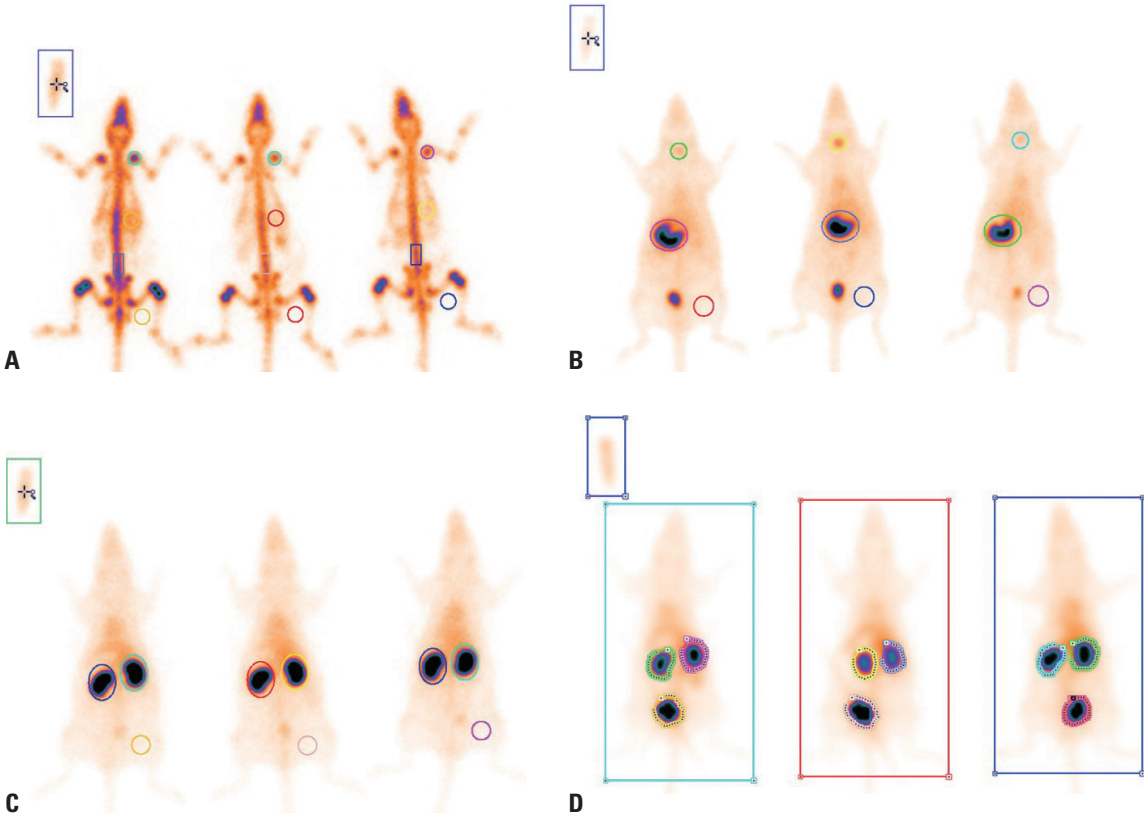

Fig. 1. ROI over the relevant organs were drawn depending on the type of radiotracer used [(A) Tc-99m HDP image, (B) Tc-99m pertechnetate image, (C) Tc-99m DMSA image, (D) Tc-99m MAG_3 image]. (A) The circles and rectangle represent ROIs of the right shoulder, liver, lumbar spine, and right buttock in order from above. (B) ROIs on the thyroid gland, stomach, and right buttock. (C) ROIs on the kidneys and right buttock. (D) ROIs on the kidneys and bladder. All these images belong to the control group. ROI, regions of interest; HDP, hydroxy-methylene-diphosphonate; DMSA, dimercaptosuccinic acid; MAG_3, mercaptoacetyltriglycine.

randomly distributed to control (n=6) and UDCA (n=7) groups.

Images were obtained 10 min after oral administration of normal saline (500 μL, control group) or UDCA (500 μL, 10 mg, UDCA group). Before acquiring the scans, rats were anesthetized, and a 27-gauge infusion set with a 30 cm tube filled with saline supplemented with heparin (50 international units/mL) was inserted into the tail vein. Immediately after starting the dynamic image acquisition, about 300 μL (74 MBq, 2 mCi) of Tc-99m MAG_3 was infused, followed by flushing with 700 μL of normal saline. Dynamic images were acquired for 30 min at a rate of 1 frame per second, resulting in a total of 1800 scans.

Images were analyzed by drawing ROIs over the total body, both kidneys, and the bladder. The ROI of the total body was 110.7×211.2 mm and that of the standard point source was a 27.2×52.4 mm rectangle. The ROIs over both kidneys and bladder were drawn along the outlines of the organs (Fig. 1D).

Soft tissue radioactivity was calculated by subtracting the radioactivity of both kidneys and the bladder from TBA. Since there might be functional differences between the left and right kidneys, the sum of both kidney counts was used for image analysis and for calculating the time to peak renal activity (T_{max}) and half-time of renal activity ($T_{1/2}$). Radioactivity and radioactivity/[radioactivity/TBA (%)] of the soft tissue, both kidneys, and the bladder were compared.

Statistical analysis

All data are presented as a mean±standard deviation. All image parameters and total body activity of both groups were compared using the Mann-Whitney U test (SPSS ver. 23; IBM Corp., Armonk, NY, USA). A *p* value of less than 0.05 was considered statistically significant.

RESULTS

Net injection dose and total body radioactivity measured using a dose calibrator

Net ID was calculated by subtracting the radioactivity that remained in the syringe after injection from the radioactivity of the radiotracer as prepared. Time correction was applied based on the injection time to calculate the Net ID. In all radiopharmaceutical experiments, Net ID values were similar between the control and UDCA groups ($p>0.05$)(Table 1). TBAs measured just after radiotracer injection were also similar between the control and UDCA groups in all experiments. The TBAs after all five image acquisition time points had elapsed were generally lower in the UDCA group, except in the Tc-99m DMSA experiment. However, there were no significant differences between the two groups ($p>0.05$)(Table 1).

Tc-99m HDP image interpretation

In image analysis of the Tc-99m HDP experiments (n=18) with 5 mg of UDCA, the rate of change (%) in buttock radioactivity was significantly different between the two study groups at 3 h–30 min and 4 h–30 min, and the buttock showed greater decreases in radioactivity in the UDCA group.

Similar effects were found in the Tc-99m experiments with 10 mg of UDCA (n=18). Buttock radioactivity was lower in the UDCA group at the 4 h time point. Liver radioactivity in the UDCA group was substantially less at 2 h–30 min, as well as 4 h–30 min, than that in the control group. Details are summarized in Table 2.

The use of 10 mg of UDCA was not associated with greater radioactivity excretion from soft tissue, compared to 5 mg of UDCA. Imaging parameters of ROIs in the lumbar spine and the right shoulder were not significantly different between the two study groups with either 5 mg or 10 mg of UDCA.

Tc-99m pertechnetate image interpretation

In image analysis of the Tc-99m pertechnetate experiments (n=12), radioactivity of the buttocks was greater in the control group at 1, 3, and 4 h. The rates of change (%) in the buttocks differed at 1 h–30 min, 3 h–30 min, and 4 h–30 min, and radioactivity in the UDCA group decreased more substantially.

The rates of change (%) in the thyroid gland were different at 1 h–30 min and 4 h–30 min, and radioactivity decreased more

Table 1. Net ID and TBA Measured by a Dose Calibrator after Image Acquisition

Group	UDCA (mg)	Net ID (kBq)	*p* value of Net ID	TBA (kBq)	*p* value of TBA
Tc-99m HDP					
Control	0	75.887±4.366		23.754±3.441	
UDCA	5	75.500±6.142	0.077	21.238±2.516	0.136
Tc-99m HDP					
Control	0	68.672±7.289		19.573±4.958	
UDCA	10	68.833±7.067	0.730	19.129±3.885	1.000
Tc-99m pertechnetate					
Control	0	74.958±5.772		32.227±3.709	
UDCA	10	74.178±5.180	0.180	29.822±3.848	0.394
Tc-99m DMSA					
Control	0	64.010±6.586		34.780±3.922	
UDCA	10	65.305±5.883	0.699	35.076±4.070	0.699

ID, injection dose; TBA, total body radioactivity; UDCA, ursodeoxycholic acid; HDP, hydroxy-methylene-diphosphonate.

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Table 2. Comparison of Parameters in the Experiments with Various Tc-99m Radiopharmaceuticals

Target organ	Parameter	Time point	Group	UDCA (mg)	Value	*p* value
Tc-99m HDP						
Buttock	Rate of change (%)	3 h–30 min	Control	0	-47.468±7.073	0.008
			UDCA	5	-57.312±5.729	
		4 h–30 min	Control	0	-56.19 5±4.881	0.024
			UDCA	5	-64.825±7.452	
Tc-99m HDP						
Buttock	Radioactivity (kBq)	4 h	Control	0	19.943±1.542	0.019
			UDCA	10	15.207±2.035	
Liver	Rate of change (%)	2 h–30 min	Control	0	-31.083±2.181	0.011
			UDCA	10	-34.525±2.627	
		4 h–30 min	Control	0	-46.010±3.402	0.024
			UDCA	10	-50.761±4.314	
Tc-99m pertechnetate						
Buttock	Radioactivity (kBq)	1 h	Control	0	404.225±22.393	0.026
			UDCA	10	316.572±8.279	
		3 h	Control	0	230.214±13.232	0.009
			UDCA	10	187.146±5.079	
		4 h	Control	0	197.654±13.032	0.015
			UDCA	10	138.158±23.372	
Thyroid gland	Rate of change (%)	1 h–30 min	Control	0	-20.558±4.958	0.041
			UDCA	10	-28.698±2.536	
		4 h–30 min	Control	0	-64.947±2.860	0.026
			UDCA	10	-71.165±4.181	
Tc-99m DMSA						
Kidney	Rate of change (%)	1 h–30 min	Control	0	-0.787±0.531	0.002
			UDCA	10	4.335±1.144	
Buttock	Rate of change (%)	3 h–30 min	Control	0	-32.456±2.826	0.065
			UDCA	10	-43.164±3.470	

UDCA, ursodeoxycholic acid; HDP, hydroxy-methylene-diphosphonate; DMSA, dimercaptosuccinic acid.

substantially in the UDCA group. Details are shown in Table 2.

Imaging parameters showed no differences between the control and UDCA groups in the stomach ROI.

Tc-99m DMSA image interpretation

In image analysis of the Tc-99m DMSA experiments (n=12), while the radioactivity of the kidneys in the control group decreases a little at 1 h–30 min, that in the UDCA group increased. These findings highlighted the accumulation of radiotracer into the kidneys in the UDCA group earlier in the experiment. Radioactivity of the buttocks decreased more in the UDCA group at 3 h–30 min, although the statistical difference was not significant. Details are presented in Table 2.

Tc-99m MAG_3 image interpretation

Time-activity curves of radioactivity in the kidneys in the two study groups were drawn and compared. Because renal function may differ between the two kidneys in the same animal, whole-kidney radioactivity was used to draw the time-activity curve. Time to peak renal activity (T_{max}) and half-time of renal activity ($T_{1/2}$) were shorter in the UDCA group (T_{max}=3.430 min; $T_{1/2}$=17.432 min) than in the control group (T_{max}=4.134 min; $T_{1/2}$=23.321 min). T_{max} and $T_{1/2}$ are shown on the kidney time-activity curve in Fig. 2A.

Meanwhile, radioactivity and radioactivity/TBA (%) values for soft tissue, both kidneys, and the bladder were compared at the time points of 2, 5, 10, 15, 20, 25, and 30 min. At 2 min, radioactivity and radioactivity/TBA (%) of the kidneys were greater in the UDCA group than in the control group, which suggested early accumulation of Tc-99m MAG_3 in the kidneys in the UDCA group, similar to the Tc-99m DMSA experiments (Tc-99m MAG_3 kidney radioactivity, control:UDCA=16.361±1.456 MBq:19.000±1.477 MBq, p=0.014; kidney radioactivity/TBA(%), control:UDCA=33.639±3.000%:36.882±1.515%, p=0.035).

At 5 and 10 min, radioactivity/TBA (%) values for soft tissue in the UDCA group were lower than those in the control group (5 min, control:UDCA=52.907±3.292%:48.215±1.063%, p=0.001; 10 min, control:UDCA=40.051±4.344%:36.066± 2.529%, p=0.022). At 15 min, radioactivity/TBA (%) values for soft tis-

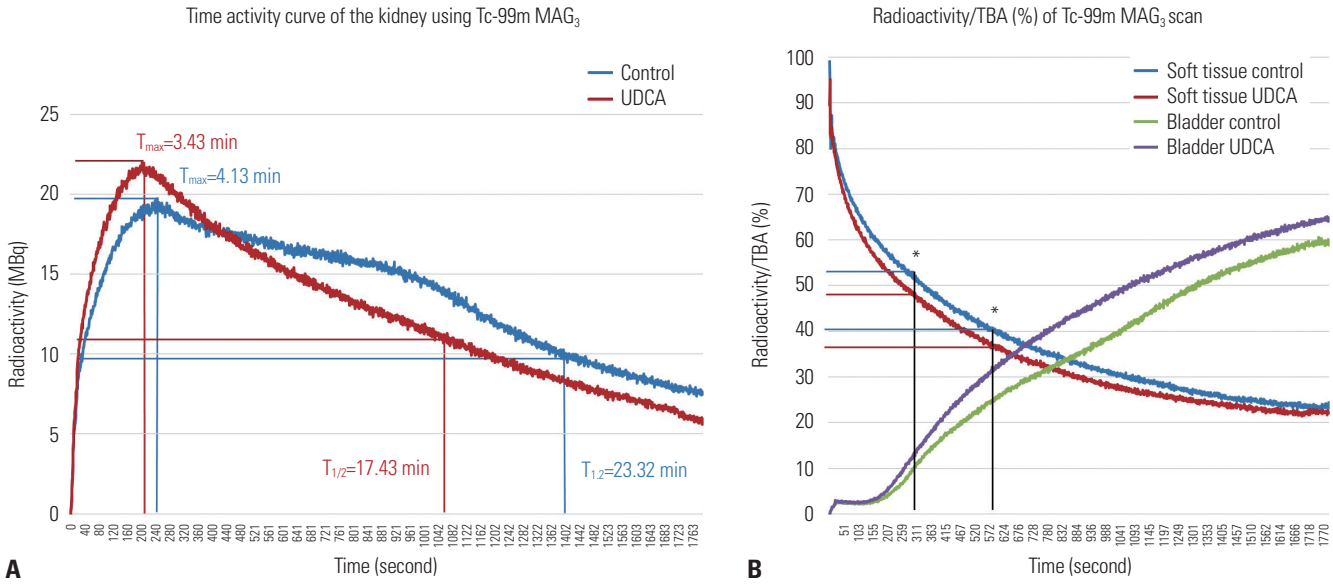

Fig. 2. Time activity curve of the kidney and Radioactivity/TBA(%) using Tc-99m MAG_3. (A) The time activity curves of the kidneys from the two groups were compared. Time to peak renal activity (T_{max}) and half-time of renal activity ($T_{1/2}$) were shorter in the UDCA group (T_{max}: 3.43 min, $T_{1/2}$: 17.43 min) than in the control group (T_{max}: 4.13 min, $T_{1/2}$: 23.32 min). (B) Radioactivity/TBA (%) curves from Tc-99m MAG_3 scans show earlier excretion of radioactivity from the soft tissue in the UDCA group. *Statistical significance. UDCA, ursodeoxycholic acid; MAG_3, mercaptoacetyltriglycine; TBA, total body activity.

sue in the control group were somewhat higher than those in the UDCA group, although the difference was not statistically significant (15 min, control:UDCA=32.793±3.986%: 29.532±2.793%, p=0.051). At 20, 25, and 30 min, there was no difference between the two study groups in radioactivity and radioactivity/TBA values for soft tissue, both kidneys, and the bladder. Fig. 2B demonstrates the radioactivity/TBA (%) curves for the soft tissue and bladder.

Net ID and peak radioactivity values for the kidneys did not differ between the two study groups (Net ID, control:UDCA= 51.282±1.998 MBq:52.392±1.110 MBq; peak radioactivity of the kidneys, control:UDCA=19.729±3.279 MBq:22.036±3.008 MBq).

DISCUSSION

UDCA, 3α, 7β-dihydroxy-5β-cholan-24-oic acid, is normally present in the human bile acid pool at a concentration up to 4%; it is formed by 7β-epimerization of chenodeoxycholic acid in the colon by a bacterial enzymatic reaction.[2] UDCA reportedly increases the hydrophilicity of the bile acid pool and bile flow, as well as exerting immune-suppressive effects.[10-12] After oral administration of UDCA, about 90% of a therapeutic dose is absorbed in the small bowel and enters the portal circulation.[13] Subsequently, it undergoes efficient extraction from portal blood by the liver. First-pass extraction from the portal blood ranges from 50–70%.[14] In the liver, UDCA is conjugated with either glycine or taurine and excreted into the bile.[15] UDCA in bile juice accumulates in the gallbladder and is expelled into the duodenum. In the small intestine, some conjugated UDCA is deconjugated and reabsorbed in the terminal ileum.[14] Small quantities of UDCA appear in the systemic circulation due to its high first-pass metabolism.[15]

The biologic half-life of orally administered UDCA in humans is quite long, estimated at 3.5 to 5.8 days, due to enterohepatic circulation.[14] After oral administration of a 500 mg tablet of UDCA to healthy volunteers, T_{max} values in plasma concentrations occur at 60 min, and a second peak concentration occurs at 180 min.[14] In the current study, most Tc-99m radiopharmaceuticals remaining in the soft tissue were present at significantly lower levels in the UDCA group at the 3 h and 4 h time points. The long time course of UDCA action is considered to be due to its long biologic half-life related to effective enterohepatic circulation.

UDCA is known to act primarily in the hepatobiliary system. In the current study, we measured liver radioactivity with Tc-99m HDP, and as expected, liver radioactivity in the UDCA group showed greater excretion than that in the control group at 2 h–30 min and 4 h–30 min.

UDCA is generally well tolerated with few side effects. Diarrhea is the main reported side effect. The incidence of diarrhea in controlled human studies was up to 3%.[14] In the current study, only a few rats showed loose stools after taking UDCA, and no rat suffered from watery diarrhea.

The mechanisms of uptake and excretion pathways of various radiopharmaceuticals are thought to be one factor affecting the action of UDCA. Tc-99m HDP, one type of Tc-99m diphosphonate radiopharmaceutical, is taken up by hydroxyapatite crystals at the surface of bone by chemisorption. This strong adsorption may make it difficult for UDCA to release Tc-99m HDP from the bones and joints. This explains why the imaging

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parameters of the lumbar spine and the right shoulder were not different between the two study groups with either 5 mg or 10 mg of UDCA. Interestingly, the time points of UDCA's effect on the radioactivity of the buttock and liver were different: In image analysis of Tc-99m HDP with 10 mg of UDCA, buttock radioactivity and radioactivity/ID (%) were lower in the UDCA group at 4 h after UDCA administration. On the other hand, the rate of change (%) in liver activity showed a difference from an early time point of 2 h–30 min. In addition to the renal excretion effect, accelerated hepatobiliary excretion of Tc-99m HDP at 2 hr after UDCA administration could contribute to the reduction in the total amount of Tc-99m HDP in the body over time. This could account for the reduction in buttock radioactivity at 4 hr.

Tc-99m pertechnetate is transported by the sodium iodide symporter; therefore, Tc-99m pertechnetate scintigraphy is a powerful imaging modality for assessing sodium iodide symporter activity in various organs.[16,17] In the present experiments, the UDCA group showed that Tc-99m pertechnetate accumulated early in the thyroid gland within 30 min and was released at a faster rate, compared to the control group. This UDCA effect was observed in the kidney radioactivity in Tc-99m MAG_3 experiments too. However, there was no difference in stomach radioactivity between the two study groups. The thyroid gland, salivary gland, and stomach are well-known organs that normally express endogenous sodium-iodide symporter. One previous study addressing the distribution and dynamics of Tc-99m pertechnetate uptake using single-photon emission computed tomography in living mice found that accumulation and efflux of Tc-99m pertechnetate were slower in the stomach than in the thyroid gland.[16] They presumed that the slower uptake and efflux rates in the stomach were linked to compartments that are proportionally larger.[16] We also think that this basic structural difference may contribute to the smaller effect of UDCA in the stomach. Although the time points until a statistical difference appeared varied, values at the buttocks and thyroid gland in the control group were always higher than those in the UDCA group from 1 hr after UDCA administration. If the experiments are conducted with a larger number of rats, significant differences may appear at all time points. Further studies with a larger number of rats are necessary.

Tc-99m DMSA scintigraphy is used to gain information on renal cortical morphology.[18-20] In the present study, we found that UDCA accelerated the accumulation of Tc-99m DMSA in the kidneys at an early time point of 1 h–30 min, and the differences in kidney radioactivity between the UDCA and control groups decreased over time. The effect of UDCA on the kidneys in the Tc-99m DMSA experiments in terms of the accumulation of radioactivity with a higher rate in the early period was similar to the effect thereof on the thyroid gland in the Tc-99m pertechnetate experiments and on the kidney in the Tc-99m MAG_3 experiments. However, unlike the Tc-99m pertechnetate and MAG_3 experiments, the UDCA effect on Tc-99m DMSA efflux from the kidneys was not different from that of the control group. Through this study, we found that the effect on excretion may differ depending on the types of radiopharmaceutical, even in the same organ. This would likely be due to differences in mechanisms of how and where radiopharmaceuticals accumulate and are excreted. Additional research is necessary to elucidate more detailed pathways.

Tc-99m MAG_3, another popular renal radiopharmaceutical, is more specific to renal excretory function.[21] In the present experiments using Tc-99m MAG_3, the effect of UDCA was also confirmed at an early stage within 15 min after acquisition (within 25 min after UDCA administration), similar to the experiment using Tc-99m DMSA. In summary, through this investigation, UDCA showed an effect at the earliest stage in the kidney, followed by an effect in the liver. Excretory effects on buttock radioactivity was observed later when the effects of the previous two organs were combined.

Various factors can affect the absorption and excretion of radiopharmaceuticals, such as a patient's clinical condition, the radiopharmaceutical preparation method, and the effects of other medicines that a patient is taking. Given the results of the current study, UDCA is thought to be an example of a medicine that affects the uptake and excretion of various radiopharmaceuticals. The locations of UDCA's impact and the substances on which UDCA act should be identified at the cellular and molecular biological level in further studies.

TBA measured by a dose calibrator after image acquisition was also generally lower in the UDCA group, except in the Tc-99m DMSA experiment. T_{max} and $T_{1/2}$ obtained in the Tc-99m MAG_3 experiment were also shorter in the UDCA group (T_{max}: 3.430 min, $T_{1/2}$: 17.432 min) than in the control group (T_{max}: 4.134 min, $T_{1/2}$: 23.321 min). However, the differences were not statistically significant. The reason for the lack of statistical significance might be the small number of rats used. A further larger-scale experiment is necessary.

This study has several limitations. First, since we aimed to investigate the effect of UDCA on various radiopharmaceuticals, the number of rats in each radiopharmaceutical group was not large. Second, the dose-effect of UDCA was confirmed only in the Tc-99m HDP experiment using 5 and 10 mg of UDCA. Studies with more varied doses should be conducted to determine the optimal dose. Third, in the renal excretion experiment using Tc-99m MAG_3, because the time that rats could be maintained under anesthesia was limited to 30 min due to safety concerns, the pharmacological effects of UDCA after 30 min could not be investigated. Additionally, because this study confirmed the effects of UDCA by only animal experiments using rats, additional research at the cellular and molecular biological level is necessary to identify the mechanisms of action of UDCA on various Tc-99m radiopharmaceuticals. Nevertheless, to our knowledge, this is the first study to evaluate the effect of UDCA on the biodistribution and renal excretion of various Tc-99m radiopharmaceuticals.

In sum, various parameters in the buttock of the UDCA group were lower in all 3 Tc-99m radiopharmaceutical experiments. Liver activity in the Tc-99m HDP experiments and thyroid activity in the Tc-99m pertechnetate experiments were also lower in the UDCA group than the control group. However, UDCA did not affect any of the parameters in the lumbar spine or shoulder joint. Interestingly, in the Tc-99m DMSA experiments, earlier accumulation of the radiotracer into the kidneys was found in the UDCA group. The results of the Tc-99m MAG_3 dynamic study suggested that UDCA accelerated urinary excretion of Tc-99m radiopharmaceuticals and decreased the background activity of soft tissue.

In conclusion, the present study demonstrates that administration of UDCA increases renal excretion and soft tissue clearance of certain Tc-99m labeled radiopharmaceuticals. This investigation could contribute to broadening the pharmacologic application of UDCA.

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