# Comparison of the Biodistribution of Gadolinium-153 DTPA and Technetium-99m DTPA in Rats

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Twenty-three mature Sprague-Dawley male and female rats were simultaneously injected with trace quantities of [$^{153}$Gd]DTPA and [$^{99m}$Tc]DTPA and 0.5 mmol/kg of nonradioactive gadolinium DTPA. Rats were killed at 1 min, 5 min, 10 min, 15 min, and 30 min after the intracardiac bolus injection. The heart, lungs, liver, brain, kidney, and blood were excised and counted in a well-counter to determine the amount of the injected material in each organ and blood. In order for the percent of total injected activity to be determined, a technique was developed which allowed discrimination of the 140 keV gamma-ray of $^{99m}$Tc from sum peaks of $^{153}$Gd when the latter is counted in a well-counter with $4\pi$ geometry. Although the distribution of the two DTPA compounds was qualitatively similar, statistical analysis indicated that the amount of $^{99m}$Tc deposited in the lungs was higher than $^{153}$Gd ($p = 0.03$), the amount of $^{99m}$Tc deposited in the kidneys was lower than $^{153}$Gd ($p = 0.0004$) and the amount of $^{99m}$Tc in the blood was higher than $^{153}$Gd ($p = 0.0022$). This may be due to the greater binding of [$^{99m}$Tc]DTPA or its minor impurities to plasma proteins.

**J Nucl Med 29:1683–1687, 1988**

The rare earth element gadolinium (Gd), when chelated to diethylenetriaminepentaacetic acid (DTPA), is showing promise as a magnetic resonance imaging (MRI) contrast agent because it is a strong paramagnetic complex, has good chemical stability, and produces minimal toxicity (*1,2,3*). Optimizing the use of this contrast agent for MRI is dependent on an understanding of its biodistribution and clearance. We decided to evaluate its distribution in comparison with that of technetium-99m DTPA ([$^{99m}$Tc]DTPA) for two reasons: a) $^{99m}$Tc is an easily employable radioactive tracer without the considerable radiation protection problems associated with $^{153}$Gd (the only radioisotope of gadolinium easily employed for radiotracer investigations) and, b) since a considerable amount is known about the biodistribution [$^{99m}$Tc]DTPA (*4*), much could be inferred regarding [Gd]DTPA if the distribution of these two chelates were quantitatively similar, e.g., gamma camera imaging could be employed for the evaluation of the clearance of these chelates from a variety of tissues. Others have suggested that the biodistribution of [Gd]DTPA is similar to the biodistribution of [$^{99m}$Tc]DTPA, i.e., it distributes into the extracellular space and is cleared by the kidneys through glomerular filtration (*5–8*). However, these data are more qualitative than quantitative. Therefore, we decided to investigate the biodistribution following a bolus injection of [$^{153}$Gd]DTPA, [$^{99m}$Tc]DTPA, and [Gd]DTPA.

Received Oct. 26, 1987; revision accepted Apr. 19, 1988.

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## MATERIALS AND METHODS

### Preparation of DTPA Solutions

Gadolinium DTPA was provided to us by Schering-Berlex, Berlin, West Germany. The radioactive tracer [$^{153}$Gd]DTPA was made in our radiopharmaceutical laboratory from $^{153}$Gd chloride and a stock solution of DTPA by a technique similar to that published by Weinmann et al. (*1*). The [$^{99m}$Tc]DTPA was prepared from an in-house radiopharmaceutical kit formulation. The freeze-dried DTPA kit contains 25.3 mg $CaNa_3$-DTPA and 1 mg stannous chloride dihydrate.

Instant thin layer chromatography of the radioactive chelates done at 1, 45, 60, 75, 90, and 105 min after mixing [$^{153}$Gd]DTPA, [$^{99m}$Tc]DTPA and [Gd]DTPA indicated that the amount of free $^{99m}$Tc and $^{153}$Gd was <2% and 1%, respectively.

**Biodistribution**

Twenty-three mature (~300 g in weight) Sprague-Dawley rats were initially anaesthetised with an intraperitoneal injection of pentobarbital (50 mg/kg). They were then injected with 0.5 mmol per kg of gadolinium DTPA [this is comparable to that employed for MRI (*2,6,7*)] and 150 $\mu$Ci per kg of [$^{99m}$Tc]DTPA and 60 $\mu$Ci per kg of [$^{153}$Gd]DTPA by direct intra-cardiac injection. All three chelates were mixed together prior to the injection so that the biodistribution of [$^{99m}$Tc] DTPA and [$^{153}$Gd]DTPA could be obtained from the same injection. Animals were then killed by an intra-cardiac injection of potassium chloride (5 mEq in 1 ml) at 1, 5, 10, 15, and 30 min after the bolus injection. Heart, lungs, liver, brain, kidney, and blood were immediately harvested and placed into 10 mm internal diameter conical test tubes for the determination of the amount of $^{99m}$Tc and $^{153}$Gd present using NaI(Tl) scintillation counting. In all cases but the liver, the entire organ was counted. For the liver, only one part was counted and then the counts were multiplied by the ratio of the total liver weight to the weight of that portion of the liver which was counted. Only 1 ml of blood was counted and therefore the reported percent injected does not reflect the total amount in the blood.

**Scintillation Counting Technique**

The percent of total injected activity of $^{153}$Gd and $^{99m}$Tc in the five organs and per ml of blood were determined using the following counting techniques. Initially, to determine the amount of radioactivity injected, a 2-in NaI(Tl) scintillation probe was used to count the syringe containing the radioactivity prior to and after injection. This was done in a fixed geometry with the detector some 20 cm remote from the syringe. The detector was cross-calibrated with standards to the NaI(Tl) well-counter used to count the tissue and blood samples. The same geometry in the well-counter was used to count these standards as was used for the tissue and blood samples.

The harvested samples were then counted in this well-counter (LKB Wallac, 1282 Compugamma, Turku, Finland) which employed a 3 in × 3 in NaI(Tl) crystal with a well 20 mm in diameter and 50 mm deep having an aluminum wall thickness of 0.3 mm. The technical difficulty associated with simultaneous counting of $^{99m}$Tc and $^{153}$Gd in $4\pi$ geometry is that the $^{153}$Gd gamma-rays and 40 keV europium x-rays coincidence sum to produce a strong peak at ~140 keV which is then confused with the 140 keV gamma-ray of $^{99m}$Tc. A copper sleeve with a wall thickness of 1.5-mm was placed between the sample 1.5-mm and the NaI(Tl) well-counter. The attenuation coefficient for copper for 40 and 100 keV photons (*9*) indicates that the intensities of the coincidence summing will be significantly reduced with the copper sleeve. Figure 1 shows two spectra of $^{153}$Gd obtained with the well-counter with and without the copper sleeve. The lower energy window was set between 40 and 120 keV and the upper energy window was set between 144 and 193 keV. The presence of the copper sleeve reduced the events in the upper energy window as a percent of those in the lower energy window from 32 to 3%. This setting of the lower bound of the upper energy window insured that no $^{153}$Gd gamma-rays (maximum energy of gamma-ray with appreciable abundance is 103 keV) would be counted in the $^{99m}$Tc window. This was found to be effective even though the number of 140 keV photons of $^{99m}$Tc detected was reduced by approximately a factor of two.

Prior to counting the tissue and blood samples in the well-counter, two reference samples, one containing only $^{153}$Gd and one only $^{99m}$Tc, were counted to allow calibration of down- and up-scatter correction using standard methods (*10*). All these reference samples and all the tissue and blood samples were counted with the copper sleeve in place. In this way we have been able to determine the percent of the injected dose of $^{99m}$Tc and $^{153}$Gd sequestered in the organs and per ml of blood of the killed rats. We have further assumed that the ratio of [$^{153}$Gd]DTPA and [Gd]DTPA in the injection is the same in the organ and blood samples.

**Statistical Analysis**

Five rats were killed at 1 min, 5 min, 10 min, and 15 min and three rats were sacrificed at 30 min after the intracardiac bolus injection. For each tissue, or, for each 1 ml of blood from each rat, the percent $^{99m}$Tc injected and the percent $^{153}$Gd injected was determined. Student's paired t-test was used to determine if the difference between the percent of the injected dose distributed in each organ or blood was different for $^{153}$Gd and $^{99m}$Tc. With only five or three animals per time period, it was not statistically sound to evaluate differences within a particular time period. However, there were sufficient numbers to determine whether there were significant differences in deposition when all the results of percent injected dose were grouped together for a particular organ or blood independent of the time of the killing (*11*), i.e., the difference in the percent injected within the same animal was compared for all 23 animals independent of the time of sacrifice. In this way, it was possible to determine if the percent of injected $^{99m}$Tc is significantly different from the percent injected $^{153}$Gd sequestered in any organ or blood independent of the time after injection.

## RESULTS

The results are shown in Table 1. For each time period, the percent injected dose is shown as a mean plus/minus one standard deviation (±s.d.) for the five or three animals at that time period. The mean ±s.d. is also shown for all 23 animals for each organ and isotope. The results of the Student's paired t-test along with the significance level is shown in the last two columns. Under the difference column, is the mean ± s.d. of the difference between the percent injected $^{153}$Gd less percent injection $^{99m}$Tc computed for each animal for each organ or blood. Note that the s.d. for the differences are much lower than that for either $^{99m}$Tc or $^{153}$Gd. This implies that the large s.d. in the percent uptake is related to differences between each animal which probably relate to differences in actual time of death (cessation of cardiovascular function), error in the determination of the total amount injected (some of the injected material may not have been intra-cardiac) or variation in glomerular filtration (effects of animal anaesthesia). The advantage of our technique is that such errors in the determination of the amount

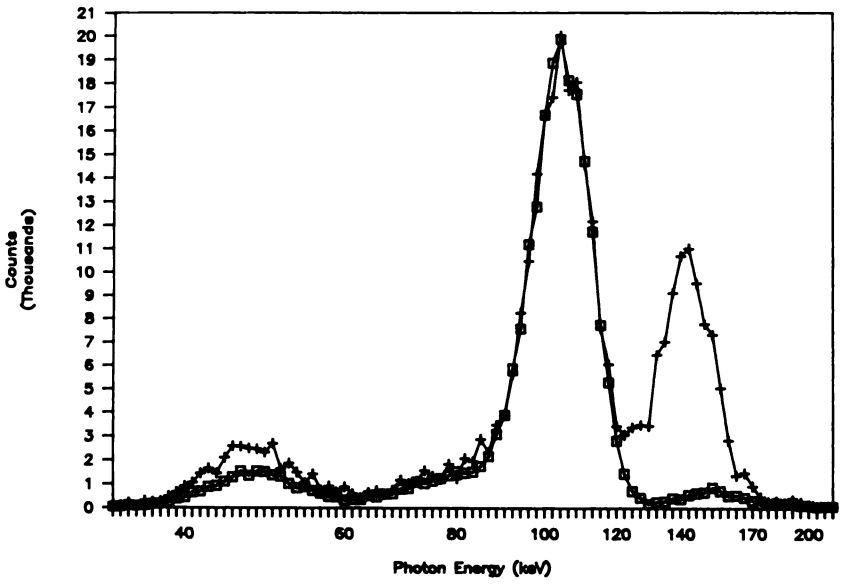


**FIGURE 1**
$^{153}$Gd spectrum with (□) and without (+) 1.5 mm of copper filtration taken using a well-counter employing $4\pi$ geometry. The spectra were normalized by equalizing the area under the spectra from 97 keV to 120 keV.

injected is eliminated when comparing the amounts of $^{153}$Gd and $^{99m}$Tc within the same animal. The differences in percent deposited in the heart, liver, and brain were found not to be statistically significant, whereas the amount of $^{99m}$Tc deposited in the lungs was significantly higher than $^{153}$Gd ($p = .030$). The amount of $^{99m}$Tc deposited in the kidneys was significantly lower than $^{153}$Gd ($p = .0004$). However, in the blood, the amount of $^{99m}$Tc was significantly higher than $^{153}$Gd ($p = .0022$).

## DISCUSSION

The greater $^{99m}$Tc in the lung and the blood as compared to $^{153}$Gd, along with the smaller amount seen in the kidneys, may be due to a greater plasma protein binding of [$^{99m}$Tc]DTPA as compared to [Gd]DTPA and [$^{153}$Gd]DTPA. Other investigators have reported that the blood clearance of [$^{99m}$Tc]DTPA is slightly less than that found for [$^{111}$In]DTPA (*12*), [$^{51}$Cr]EDTA (*13*), and [$^{169}$Yb]DTPA (*14*). Most authors postulate that the slower clearance is due to a greater plasma protein binding found for the [$^{99m}$Tc]DTPA preparation possibly due to impurities (*15*). An increased plasma protein binding for our [$^{99m}$Tc]DTPA would decrease the amount cleared by the kidney compared to [Gd] DTPA and thereby lead to the higher blood levels that we have observed.

However, it should be stressed that the distribution of [Gd]DTPA is very similar to that of [$^{99m}$Tc]DTPA, implying that it distributes to the extracellular space, i.e., both the vascular and extravascular space. This is consistent with what has been reported in a canine model (*8*) in which [$^{153}$Gd]DTPA concentrations in liver and blood were measured after a bolus injection but somewhat at odds to what has recently been reported in work performed on rats (*16*). In this work, [Gd]DTPA concentrations in rat plasma, liver, kidney, and spleen were determined using x-ray fluorescence. Barnhardt et al. (*16*) report kidney and plasma clearances of a bolus injection of [Gd]DTPA at 5, 15, and 30 min similar to our results but measure very little activity in the liver. In fact, they propose that [Gd] DTPA is distributed primarily in the vascular compartment and do not comment about its possible distribution in the extracellular/extravascular space. In contrast, Boudreau et al. (*8*) show a liver clearance curve of [$^{153}$Gd]DTPA similar to ours at 1, 15, and 30 min. It is difficult to reconcile these differences based on the contrary material presented in these reports. However, it should be pointed out that Pettigrew et al. (*7*) have shown that a bolus injection of [Gd]DTPA does alter the signal intensity in MR images of the liver and consequently state that [Gd]DTPA has value as a hepatic contrast agent. This is contrary to the work of Barnhardt et al. (*16*) who claim that [Gd]DTPA has no potential as a liver contrast agent. We can only speculate that [Gd]DTPA liver concentrations may not be accurately determined using x-ray fluorescence.

We believe that [Gd]DTPA distributes to the entire extravascular space. Therefore the contrast enhancement of MR images after a bolus injection of [Gd] DTPA will initially be related to the amount of [Gd] DTPA delivered to that organ (i.e., contrast dependent on organ blood flow) and as time progresses, will be related to the size of the organ's extracellular space and the excretion of [Gd]DTPA from the body by renal filtration (i.e., glomerular filtration rate).

In summary, the biodistribution of [Gd]DTPA is similar to [$^{99m}$Tc]DTPA in heart, liver, and brain. However, some deviation in the biodistribution of these compounds has been seen in lung, kidney, and blood.

**TABLE 1**
**Biodistribution of $^{99m}$Tc and $^{153}$Gd**

| | Percent of Injected Radioisotope | | | | | | Mean of difference (n = 23) | P-value |
|---|---|---|---|---|---|---|---|---|
| | 1 min (n = 5) | 5 min (n = 5) | 10 min (n = 5) | 15 min (n = 5) | 30 min (n = 3) | Total (n = 23) | | |
| Heart | | | | | | | | |
| $^{99m}$Tc | 1.63 ± 0.86 | 0.963 ± 0.452 | 0.808 ± 0.300 | 0.939 ± 0.369 | 0.413 ± 0.023 | 0.997 ± 0.598 | | |
| $^{153}$Gd | 1.79 ± 1.12 | 0.883 ± 0.409 | 0.653 ± 0.214 | 0.842 ± 0.318 | 0.357 ± 0.065 | 0.953 ± 0.720 | −0.0446 ± 0.2186 | 0.340 |
| Lungs | | | | | | | | |
| $^{99m}$Tc | 3.39 ± 0.39 | 2.44 ± 1.08 | 2.09 ± 0.65 | 5.92 ± 4.90 | 2.74 ± 1.72 | 3.367 ± 2.656 | | |
| $^{153}$Gd | 3.38 ± 0.48 | 2.49 ± 1.21 | 1.81 ± 0.41 | 5.32 ± 4.44 | 2.35 ± 0.95 | 3.134 ± 2.381 | −0.233 ± 0.480 | 0.030 |
| Liver | | | | | | | | |
| $^{99m}$Tc | 8.97 ± 4.32 | 4.60 ± 1.04 | 5.08 ± 0.72 | 5.90 ± 1.52 | 3.55 ± 1.28 | 5.799 ± 2.771 | | |
| $^{153}$Gd | 9.82 ± 4.49 | 4.13 ± 1.01 | 4.59 ± 0.38 | 6.71 ± 2.47 | 3.68 ± 1.26 | 5.969 ± 3.246 | 0.170 ± 1.037 | 0.44 |
| Brain | | | | | | | | |
| $^{99m}$Tc | 0.131 ± 0.049 | 0.172 ± 0.082 | 0.138 ± 0.038 | 0.0716 ± 0.0404 | 0.114 ± 0.107 | 0.1262 ± 0.0669 | | |
| $^{153}$Gd | 0.136 ± 0.053 | 0.186 ± 0.072 | 0.131 ± 0.039 | 0.0728 ± 0.0387 | 0.120 ± 0.120 | 0.1299 ± 0.0691 | 0.00363 ± 0.0117 | 0.15 |
| Kidney | | | | | | | | |
| $^{99m}$Tc | 7.11 ± 2.65 | 10.2 ± 5.55 | 11.8 ± 3.58 | 6.22 ± 6.02 | 5.61 ± 6.86 | 8.420 ± 5.100 | | |
| $^{153}$Gd | 8.10 ± 2.90 | 11.4 ± 6.58 | 12.7 ± 4.03 | 6.78 ± 6.98 | 6.99 ± 9.15 | 9.375 ± 5.906 | 0.955 ± 1.090 | 0.0004 |
| Blood | | | | | | | | |
| $^{99m}$Tc | 4.22 ± 1.63 | 3.16 ± 1.66 | 2.65 ± 3.35 | 1.53 ± 0.78 | 1.11 ± 0.12 | 2.679 ± 2.076 | | |
| $^{153}$Gd | 3.83 ± 1.00 | 2.78 ± 1.36 | 2.14 ± 2.62 | 1.37 ± 0.80 | 0.988 ± 0.277 | 2.340 ± 1.700 | −0.3387 ± 0.4679 | 0.0022 |

* This is the mean (n = 23) of the difference in the percent injected of $^{153}$Gd less the percent injected of $^{99m}$Tc in the same animal.

This is probably due to greater plasma protein binding of [$^{99m}$Tc]DTPA itself or some contaminant associated with [$^{99m}$Tc]DTPA (*15*) in comparison to [Gd]DTPA. Therefore, it is inappropriate to determine the biodistribution of [Gd]DTPA using the tracer [$^{99m}$Tc]DTPA in the lung, kidney, and blood.

## ACKNOWLEDGMENTS

This work was supported in part by a grant (MA-9467) from the Medical Research Council of Canada to FSP and by a grant (AN 765) from the Canadian Heart and Stroke Foundation to GW. The authors thank Mr. John Parr for typing and editing the manuscript and Mrs. Helen Cheung for statistics consulting.

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