

PRELIMINARY NOTE

Differential Renal Function Using Technetium-99m Dimercaptosuccinic Acid (DMSA): In Vitro Correlation

Michael J. Daly*, William Jones, Thomas G. Rudd, and James Tremann

University of Washington and Veteran's Administration Hospital, Seattle, Washington

The relationship between differential renal uptake of Tc-99m 2-3 dimercaptosuccinic acid (DMSA) and differential renal function was examined in normal and abnormal dogs by correlating Tc-99m DMSA localization with relative renal blood flow and creatinine clearance. There was close correlation of fractional Tc-99m DMSA localization with relative renal function.

J Nucl Med 20: 63-66, 1979

Several radiopharmaceuticals have been used to display renal anatomy and to estimate individual renal function. The search for a single agent that could perform both of these tasks has had limited success. Although renography with I-131 Hippuran can provide a dynamic qualitative indication of renal function with available gamma cameras, more sophisticated computer equipment is required to estimate individual renal function. In addition, the dynamic nature of the renogram and the suboptimal energy of I-131 make it difficult to display detailed renal anatomy. Mercury-labeled compounds have been used until recently to visualize the renal parenchyma. Raynaud and other investigators, using $^{197}\text{HgCl}_2$ and [^{197}Hg] chlormerodrin, emphasized the functional data obtainable with these imaging agents (1,2). However, even before the introduction of technetium-99m-labeled pharmaceuticals, the

mercury agents had not gained wide acceptance because the 6277-keV energy of Hg-197 is poorly suited to gamma cameras, Hg-203 has unfavorable dosimetry, and both required a 24- to 48-hr delay before scanning. The chelate 2-3 dimercaptosuccinic acid (DMSA) was used originally in gram amounts to treat heavy-metal poisoning (3). When complexed with Tc-99m, DMSA shows greater renal concentration than other technetium-labeled agents (4). The biologic behavior of Tc-99m DMSA is similar to that of chlormerodrin, showing predominantly cortical localization and only slight urinary excretion (5). Lack of significant urinary concentration permits better definition of renal structure and comparison between the kidneys of relative concentration of the Tc-99m DMSA without interference from activity in the pelvo-calyceal structures.

Clinical reports have already documented the excellent imaging characteristics of Tc-99m DMSA (6,7). Considering its similarity to chlormerodrin, we decided to evaluate Tc-99m as an indicator of renal function by comparing relative Tc-99m DMSA localization with differential creatinine clearance and relative renal blood flow (RBF) in an animal model.

*Present address: University of Arizona Health Sciences Ctr., Div. of Nuclear Medicine, Tucson, AZ 85724.

Received Feb. 22, 1978; revision accepted Aug. 10, 1978.

For reprints contact: Michael J. Daly, University of Arizona Health Sciences Ctr., Div. of Nuclear Medicine, Tucson, AZ 85724.

MATERIALS AND METHODS

Our model involved 14 mongrel dogs, divided into two categories: five control animals and nine with unilateral renal disease. The latter were subdivided into three dogs with acute arterial stenosis and six dogs with unilateral ureteral obstruction of variable duration, followed by re-anastomosis and a similarly variable recovery period. The reason for the diversity of both types of renal injury and recovery periods was to produce a spectrum of unilateral renal damage ranging from mild to severe.

Acute, partial renal-artery stenosis was accomplished on the day of the study in three dogs. A baseline left renal-artery flow rate was measured with an electromagnetic flow probe. A constrictor was then placed proximal to the flow probe and adjusted to reduce the renal blood flow to <50% of the baseline throughout the study.

The distal right ureter was ligated to cause unilateral hydronephrosis. One to three weeks of complete obstruction were allowed before removal of the ligation and re-anastomosis by a uretero-neocystostomy. A 1-6 week recovery period followed.

At the time of the study, anesthesia was obtained by i.v. pentobarbital (30 mg/kg) with respiration supported by a Harvard pump connected to an endotracheal tube. Both ureters were cannulated by means of a mid-line abdominal incision, and bilateral femoral-vein cutdowns were performed for infusion and blood sampling. Following a saline-induced diuresis, exogenous creatinine was administered at a primary dose of 5 g/dl at 1.5 cc/kg, followed by a sustaining solution of 0.25 g/dl to attain serum creatinine levels of 10-16 mg/dl. An i.v. injection of Tc-99m DMSA (0.25-1.0 mCi) was given. Serial urine collections and blood samples for differential creatinine clearances over a minimum of 1.5 hr were obtained to provide estimates

of differential renal function. Immediately before killing, strontium-85 microspheres, 15 μ in diameter, were injected into the left ventricle or arch of the aorta to evaluate relative renal blood flow. The kidneys were then removed.

The Tc-99m and Sr-85 activities in each kidney were measured using a flat-field collimator placed at a standard distance (44 cm) from the kidney. The contribution of Compton-scattered photons into the Tc-99m energy window was estimated with a pure Sr-85 source, and the Tc-99m counts were adjusted accordingly. The relative distribution of the Tc-99m and Sr-85 was expressed as the ratio of the activity in the left (L) kidney compared with the total activity in both kidneys (L + R), thus giving a fractional distribution or percentage in the left kidney for the total Tc-99m or Sr-85 [L/(L+R)]. The creatinine clearance was expressed in a similar manner, with the clearance of the left kidney divided by the clearance for both kidneys.

RESULTS

All whole-organ creatinine clearances, relative blood flows, and relative Tc-99m DMSA localization data are contained in Table 1. As expected, the control animals (Nos. 1-5) had equal R and L kidney functions, and blood flow was equally divided as was relative Tc-99m DMSA localization. Moderate reduction in function and blood flow characterized the models of renal-artery stenosis. Markedly impaired creatinine clearances were found in the (R) kidneys compromised by ureteral obstruction (Dogs 9-14), with the uninvolved (L) kidneys assuming up to 93% of total renal function. There was a similar reduction in blood flow to the obstructed kidney compared with the normal left kidney.

The relationships between fractional Tc-99m DMSA localization and relative blood flow, as de-

TABLE 1. FRACTIONAL Tc-99m DMSA RENAL LOCALIZATION AND RENAL FUNCTION RESULTS

	Dog No.	Left CrCl Avg (cc/min)	Right CrCl Avg (cc/min)	CrCl L/L + R	Tc-99m DMSA L/L + R	Sr-85 (RBF) L/L + R
Control	1	32.0	32.7	0.49	0.49	0.49
	2	39.1	39.9	0.49	0.50	0.49
	3	30.4	29.5	0.51	0.50	0.51
	4	35.7	31.4	0.53	0.51	0.50
	5	27.3	26.2	0.51	0.50	0.50
Left arterial occlusion	6	9.0	21.2	0.30	0.45	—
	7	31.5	47.8	0.40	0.42	0.41
	8	27.6	44.3	0.38	0.40	0.44
Right ureteral ligation	9	50.2	26.0	0.66	0.61	0.60
	10	34.2	10.9	0.76	0.71	0.60
	11	50.7	31.1	0.62	0.58	0.58
	12	38.8	18.8	0.67	0.63	0.62
	13	42.4	5.2	0.89	0.88	0.87
	14	62.3	4.7	0.93	0.91	0.89

* CrCl = creatinine clearance

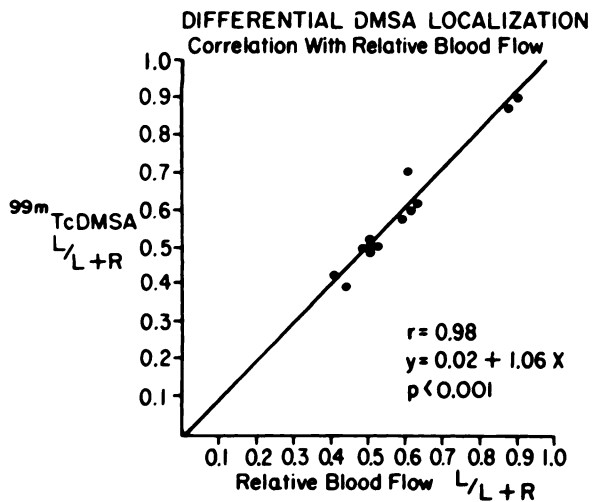


FIG. 1. Percentage of total renal blood flow, calculated from microsphere distribution, plotted against relative Tc-99m DMSA uptake. Regression line is close to line of identity.

terminated by the microsphere distribution, and relative creatinine clearance are graphically displayed in Figs. 1 and 2, with correlation coefficients of 0.98 and 0.97, respectively ($p < 0.001$). Both plots approach the line of identity, indicating a virtual one-to-one relationship between Tc-99m DMSA uptake and both relative blood flow and creatinine clearance. Elimination of the control animals (Nos. 1-5) did not significantly alter the correlation coefficients.

DISCUSSION

A noninvasive means of determining individual renal function would be advantageous in the surgi-

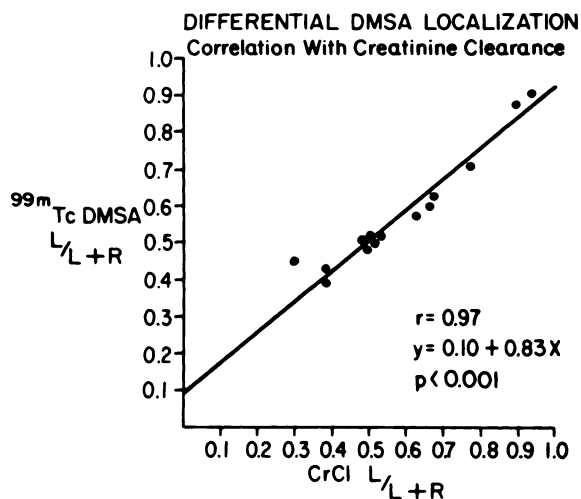


FIG. 2. Comparison of relative function of left kidney, determined by differential creatinine clearance, and relative distribution of technetium-99m DMSA.

cal or medical management of renal disease. Knowledge of how much renal function would remain postnephrectomy, for example, would be important to the urologist, while a nephrologist would benefit by being able to gauge the response of a kidney to a specific course of therapy. In the past the accepted standard to answer these questions has been the clearances derived from bilateral ureteral catheterization. This procedure requires an inpatient stay, is technically difficult, and carries significant morbidity. (8,9).

The current plethora of radionuclide techniques used both to display renal anatomy and to quantify renal function reflects the limitations of each method. Nuclear medicine approaches to measure function have ranged from the relative uptake of radiomercury-labeled chlormerodrin to more complicated mathematic manipulations of computer-acquired data using Tc-99m agents (10). The present in vitro study demonstrates the feasibility and accuracy of relative Tc-99m DMSA localization as an indicator of relative renal function. Technetium-99m DMSA uptake appears to be directly related to renal blood flow, as we have shown both by varying the renal blood flow directly in the renal-artery stenosis models, and by the direct relationship of Tc-99m distribution to renal blood flow in both control and diseased kidneys (Fig. 1). Compared with $P[^{197}\text{Hg}]$ chlormerodrin, the advantages of Tc-99m DMSA include superior energy characteristics and dosimetry, and a substantial reduction in the delay necessary before imaging. Other Tc-99m tracers used for renal imaging and functional testing have lower renal-parenchymal concentrations and significant urinary excretion, which can interfere with estimates of function (4,11). Variations in the composition of Tc-99m DMSA have been reported (12), and this might interfere in absolute uptake determinations. However, the relative distribution of Tc-DMSA should not be affected, since each kidney would accumulate the tracer, whatever its form, in proportion to that kidney's function.

In vivo quantification of Tc-99m DMSA was not attempted in this study because we believed that the distributional effectiveness of Tc-99m DMSA had to be demonstrated first with in vitro methods. Technical difficulties may be encountered in the estimation of renal function in vivo. Liver or spleen uptake may give false evaluation of renal activity, although previous reports have documented the relatively low activities in these organs (4). Variations in kidney depth, configuration, and rotation will affect measurements, independent of actual organ function. Lastly, although partial ureteral obstruction or pelvic stasis may result in false elevation of Tc-99m DMSA uptake, the low urinary excretion

of Tc-99m DMSA makes it preferable to other Tc-99m agents.

CONCLUSION

Technetium-99m DMSA is an excellent renal imaging agent with the added potential of indicating relative renal function. These preliminary data indicate that determinations of relative renal function may be feasible using Tc-DMSA. In vivo correlation in humans will be necessary to document clinical applicability and utility.

ACKNOWLEDGMENT

This work was supported in part by a General Medical Research Grant from the Veterans Administration.

REFERENCES

1. RAYNAUD C, DESGREZ A, KELLERSHOHN C, et al: Measurement of renal mercury uptake by external counting: separate functional testing of each kidney. *J Urol* 99: 248-263, 1968
2. GADBOIS WF, CORRIERE JN: The use of sequential ¹⁹⁷Hg chlormerodrin delayed scans to evaluate and to follow individual renal function. *J Urol* 112: 420-423, 1974
3. WANG SC, TING KS, WU CC: Chelating therapy with Na-

DMS in occupational lead and mercury intoxications. *Chin Med J* 84: 437-439, 1965

4. ARNOLD RW, SUBRAMANIAN G, MCAFEE JG, et al: Comparison of ^{99m}Tc complexes for renal imaging. *J Nucl Med* 16: 357-367, 1975

5. LIN TH, KENTIGAN A, WINCHELL HS: A ^{99m}Tc chelate substitute for organoradiomercurial renal agents. *J Nucl Med* 15: 34-35, 1974

6. ENLANDER D, WEBER PM, DOS REMEDIOS LV: Renal cortical imaging in 35 patients: Superior quality with ^{99m}Tc-DMSA. *J Nucl Med* 15: 743-749, 1974

7. HANDMAKER H, YOUNG BW, LOWENSTEIN JM: Clinical experience with ^{99m}Tc-DMSA (dimercaptosuccinic acid), a new renal imaging agent. *J Nucl Med* 16: 28-32, 1975

8. DAHL DS, O'CONNOR VJ, WALKER CD, et al: The morbidity of differential renal function studies. Analysis of 271 studies. *JAMA* 202: 857-861, 1967

9. FRITJOFSSON A, AURELL M: Bilateral renal clearance. Technical problems and the effect of ureteric catheterization on renal function. *Scand J Urol Nephrol* 2: 103-108, 1968

10. ASSAILLY J, PAVEL DG, BADER C, et al: Noninvasive experimental determination of the individual kidney filtration fraction by means of a dual-tracer technique. *J Nucl Med* 18: 684-691, 1977

11. CORRIERE JN, STAUM MM, GADBOIS WF, et al: Technetium ^{99m} stannous glucoheptonate for renal imaging and evaluating individual renal function. *Surg Forum* 26: 582-584, 1975

12. IKEDA I, INOUE O, KURATA K: Preparation of various Tc-99m dimercaptosuccinate complexes and their evaluation as radiotracers. *J Nucl Med* 18: 1222-1229, 1977