CLINICAL EXPERIENCE WITH ^{99m}Tc-DMSA (DIMERCAPTOSUCCINIC ACID), A NEW RENAL-IMAGING AGENT

Hirsch Handmaker, Bradford W. Young, and Jerold M. Lowenstein

Children's Hospital of San Francisco, Pacific Presbyterian Medical Center, and Letterman Army Medical Center, San Francisco, California

Results are reported from the clinical evaluation of a new radiopharmaceutical for renal imaging, ^{99m}Tc-DMSA (dimercaptosuccinic acid). Sixty-five patients were studied and six of these patients' scintiphotos are illustrated. The physical characteristics of ^{99m}Tc and the mercurial-like kinetics of the chelate produced high-resolution scintiphotos of the renal parenchyma in patients of all ages and with a variety of disease entities. The commercial availability of the material in kit form permits its usage in all nuclear medicine facilities.

A variety of radionuclide tracers have been proposed as improvements as compared with the radiomercurial compounds for renal imaging. The recent development of ^{99m}Tc-Sn-dimercaptosuccinic acid (*1*) has prompted clinical evaluation of this agent in patients of all ages and with a variety of disease processes. The results of these studies demonstrate that the agent provides superior images of renal parenchyma using a commercially available kit with virtually no undesirable urinary excretion.

MATERIALS AND METHODS

Technetium-99m-DMSA was provided in kit form (MPI Kidney Scintigraphin™ Reagent, Medi-Physics, Inc., Emeryville, Calif.). The radionuclide is an aqueous solution of 2,3-dimercaptosuccinic acid (0.547 mg/ml) and stannous chloride (0.19 mg/ml) at pH 2 to 3. In accordance with the manufacturer's suggestions, one part by volume of the DMSA reagent was added to one part by volume of oxidant-free ^{99m}Tc-pertechnetate solution and mixed thoroughly. The labeled material was incubated at room temperature for 10–20 min before intravenous administration. In all instances, the material was injected within 30 min after mixing. A dose of up to 5 mCi was used depending upon the age, sex, and size of the patient. Pediatric patients were given 50–100 μCi/kg up to a maximum of 5 mCi. No strenuous efforts were made either to hydrate patients or to have them void before injection. All patients were injected with their backs flush against the scintillation detector, "posterior" in either supine or prone position, depending upon patient's age, condition, etc. For small children the scintillation detector was placed "crystal-up" and the injection and subsequent scintiphotos made with the child supine on the detector (Fig. 1).

Received Oct. 9, 1973; revision accepted Aug. 13, 1973.

For reprints contact: Hirsch Handmaker, Nuclear Medicine Service, Children's Hospital of San Francisco, P.O. Box 3805, San Francisco, Calif. 94119.

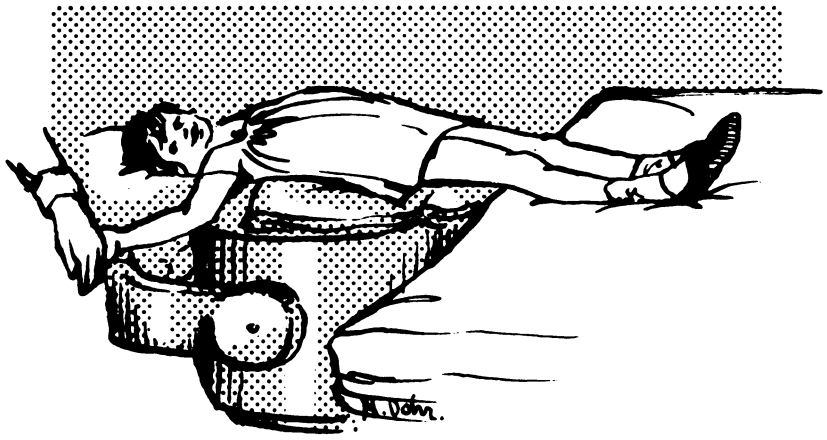

FIG. 1. Injection position for dynamic study in pediatric patients.

Six serial scintiphotos were obtained after bolus injection of the DMSA at 5–6 sec intervals commencing when the aorta was first seen on the persistence scope. A positioning static scintiphoto of 500K counts was obtained at 3 min after injection to evaluate blood pool and kidney position.

Plasma clearance of the material has been estimated at $T_{1/2}$ of approximately 45 min and about 54% of the material is localized in the rat kidney in 1 hr. Patients with normal renal function, therefore, were studied 2 hr following the injection. Patients with abnormal renal function or renal failure were studied at varying intervals up to 24 hr. Posterior renal static scintiphotos of 500K counts were made with a Searle Radiographics Pho/Gamma III/HP scintillation camera and parallel-hole high-resolution collimator or a Picker 2C Dyna Camera. These images were followed by posterior oblique scintiphotos of each kidney using a pinhole collimator and 300K counts were usually obtained at a distance of approximately 8 cm from the posterior body wall, rarely requiring more than 5 min per view. Children studied were part of a General Research Support Grant (NIH) study and appropriate consent forms were obtained from parents.

RADIATION DOSIMETRY*

Calculations are based on the absorbed-dose fraction method with the following assumptions: (A) Sixty percent of administered dose instantaneously concentrates in the renal cortex of both kidneys with no subsequent biologic clearance. (B) Thirty-three percent of the administered dose distributes instantaneously throughout the entire body with no subsequent biologic clearance. (C) Five percent of the administered dose localizes instantaneously in the liver and spleen with no subsequent biologic clearance. (D) Two percent of the administered dose is instantaneously cleared by the kidney and excreted into the bladder. These assumptions are designed to overestimate the gonadal exposure. Effective residence time in the bladder is 1 hr (Table 1).

RESULTS

Sixty-five patients were studied using the ^{99m}Tc-DMSA and a gamma scintillation camera (Table 2). In all but three patients the images obtained were of sufficient quality to satisfy the clinical question asked. Twenty-seven patients had renal studies with ^{99m}Tc-Sn-DTPA and 21 had ^{131}I-hippuran studies. In no instance was the renal image obtained with these other agents equal to or better than that obtained with the DMSA (Fig. 2). Excellent correlation was obtained in all cases compared with excretory pyelography and arteriography.

Normal renal scintigraphy. Figure 3 illustrates the normal study obtained in a 50-year-old woman who sustained abdominal trauma and was being evaluated for hematuria and suspected renal laceration. She displays what later became a constant observation in all patients studied, that of relatively "cold" areas in the medial aspect of the renal parenchyma corresponding to the area occupied by the calyces

TABLE 1. ABSORBED-RADIATION DOSE

Organ	Rad/mCi administered
Total body	0.015
Renal cortices (2)	1.400
Bladder wall	0.008
Liver	0.042
Spleen	0.067
Ovaries (2)	0.011
Testes (2)	0.006
Red marrow	0.016

* Calculations by E. M. Smith, for Medi-Physics, Inc.

TABLE 2. PATIENTS STUDIED WITH DMSA CATEGORIZED BY CLINICAL PROBLEM

Obstructive disease, hydronephrosis and/or pyelonephritis	6
Vesicoureteral reflux	4
Hypertension	10
Exstrophy, megacystis or neurogenic bladder	7
Trauma/hematuria	6
Renal mass	9
Renal failure or nonfunction on IVP	11
Congenital anomalies (polycystic, agenesis, etc.)	8
Transplant	4
Total	65

of the collecting system. Care must be taken to differentiate these structures (previously unappreciated in studies performed with other renal-imaging agents that produce less resolution) from masses, defects, or cysts in the parenchyma of the kidney.

Correlation with the IVP appearance of the pelvicalyceal system serves to emphasize this appearance and prevent erroneous overinterpretation of the renal scintigram.

Perhaps the most surprising and striking of all the patients studied were those with *pyelonephritis* either related to vesicoureteral reflux, obstructive disease, or of unknown cause. It has been suggested that the use of radionuclide scintigraphy may be valuable in the evaluation of acute and chronic pyelonephritis (*2*) and in five patients with this disease cortical defects and scars were clearly seen. In two of these patients the changes seen on the scintigrams were more severe than was suggested by the contrast pyelogram. Figure 4 is the study performed in an 11-year-old boy with recurrent left vesicoureteral reflux and pyelonephritis. Images were obtained 2 hr following the injection of 2 mCi of the ^{99m}Tc-DMSA using the high-resolution and pinhole collimator techniques described previously. The right kidney was interpreted as normal. The left kidney shows cortical thinning of the parenchyma and obvious broad-based defects in the periphery of the kidney and an irregular pattern of localization of the material throughout the renal parenchyma. Figure 5 shows the results in a 15-year-old boy who had bilateral implantations of his ureters into the sigmoid colon for bladder exstrophy with later bilateral hydronephrosis and chronic pyelonephritis. The marked deformity and scarring of the cortex characteristic of pyelonephritis is clearly demonstrated.

Figure 6 shows one of the two patients studied to evaluate their *polycystic renal disease.* The patient is a 53-year-old woman with known polycystic liver and renal disease. The DMSA scintiphotos clearly show the numerous bilateral cystic structures and enlargement of the left kidney.

Nine patients were studied in their workups for suspected *renal tumors, cysts, or abscesses.* In five of these patients the abnormal kidney did not take

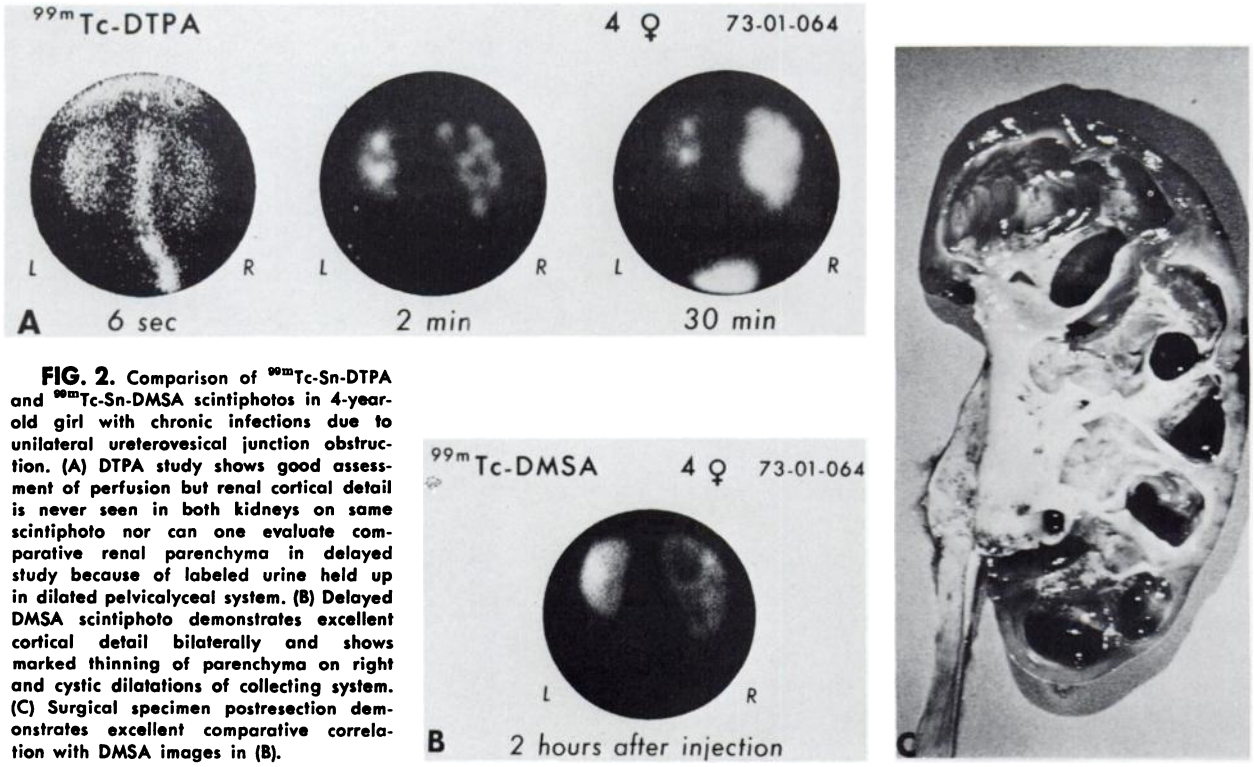

FIG. 2. Comparison of ^{99m}Tc-Sn-DTPA and ^{99m}Tc-Sn-DMSA scintiphotos in 4-year-old girl with chronic infections due to unilateral ureterovesical junction obstruction. (A) DTPA study shows good assessment of perfusion but renal cortical detail is never seen in both kidneys on same scintiphoto nor can one evaluate comparative renal parenchyma in delayed study because of labeled urine held up in dilated pelvicalyceal system. (B) Delayed DMSA scintiphoto demonstrates excellent cortical detail bilaterally and shows marked thinning of parenchyma on right and cystic dilatations of collecting system. (C) Surgical specimen postresection demonstrates excellent comparative correlation with DMSA images in (B).

FIG. 3. Normal ^{99m}Tc-DMSA scintiphotos.

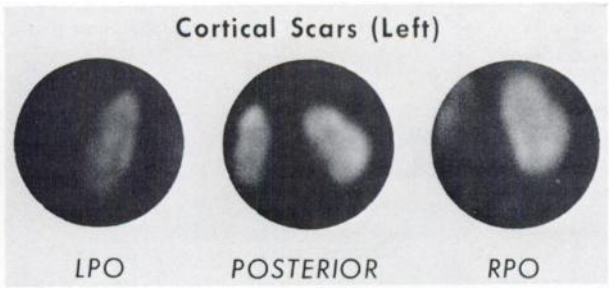

FIG. 4. Unilateral pyelonephritis secondary to reflux (11-year-old boy).

up the DMSA at all and two of three demonstrated a "cold" area in the region of the kidney in the perfusion (blood pool) and early static scintiphotos rather than the "blush" characteristically associated with hypernephromas. This suggests either avascularity due to extension of the tumor into renal vessels with occlusion or an "autonephrectomized" kidney (Fig. 7).

Figure 8 shows the study performed in a 26-year-old woman being evaluated for possible renal abscess. The pinhole oblique view of her left kidney showed a defect on the cortex extending from the periphery

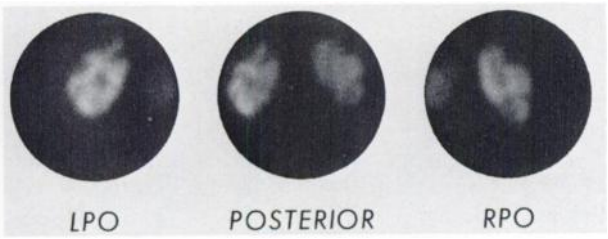

FIG. 5. Bilateral pyelonephritis (15-year-old boy).

FIG. 6. Polycystic renal disease (53-year-old woman).

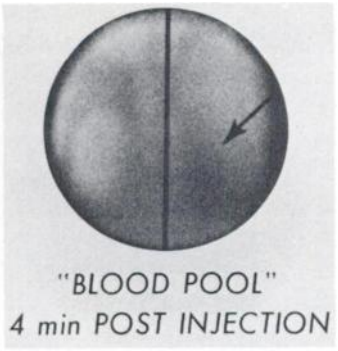

FIG. 7. Normal blood pool in left kidney, "cold" right renal bed compatible with "autonephrectomy".

well into the region of the renal pelvis. Drip infusion nephrotomogram showed a cortical mass with suggestion of pelvic extension. At surgery the patient was found to have a renal abscess that corresponded in location to the scintiphotographic appearance.

Six patients were evaluated for *hematuria* and all found to have normal renal scintiphotos. The presenting diagnoses were: trauma, possible medullary sponge kidney, suspected renal infarction due to subacute bacterial endocarditis, and suspected renal involvement with polyarteritis nodosa. All were later signed out with no apparent renal abnormalities.

Eleven patients were referred for evaluation of the presence and integrity of their kidneys as part of their workup for severe *chronic renal disease* or failure. Patients were sent because of their poor renal visualization by all other conventional means (i.e., IVP, nephrotomography). In four of five patients with blood urea nitrogens greater than 100 mg/100 ml and serum creatinines in excess of 5 mg/100 ml approximation of renal presence and size could be made. One of these patients is seen in Fig. 9. The patient who could not be visualized had a creatinine of 16 and a BUN that reached 210. It was found that in these patients static images frequently needed to be delayed to 6–10 hr after injection to allow for

FIG. 8. Renal abscess (26-year-old woman).

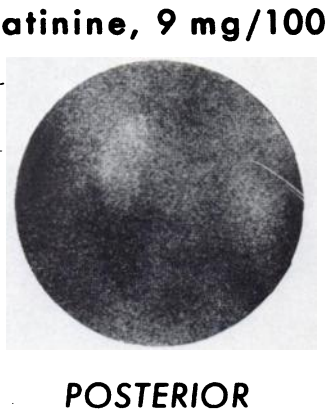

FIG. 9. Renal failure (22-year-old woman); etiology undetermined.

sufficient blood clearance to permit renal imaging. Sufficient counts exist at 24 hr to permit imaging at that time when necessary, which may be desirable in some cases.

DISCUSSION

As indicated by the variety of agents evaluated for renal imaging in the past decade (*3–12*), no one compound has been found to be ideal. It seems clear that the ^{99m}Tc compounds have decided advantages because of their physical characteristics, well known to nuclear physicians. Difficulties have arisen as a result of the chemical forms of these compounds with regard to availability, difficulty in preparation, high soft-tissue background, urinary excretion, or poor handling in patients with altered renal function. In our opinion, many of these difficulties have been reduced or eliminated with the use of ^{99m}Tc-DMSA.

Evaluation of vascular supply to the kidneys, followed by a 2-hr delay in patients with normal renal function, affords excellent appraisal of cortical detail and anatomy. As with the mercurials, TPAC, true iron ascorbate complexes, and caseidin, no significant renal excretion of the DMSA is seen during the imaging time period, preventing confusion of parenchyma with collecting system structures and affording a clear look at the cortex.

Using the high-resolution collimator and posterior pinhole oblique views, very high-resolution images of the renal structures can be obtained. In patients with severe chronic renal disease the cortical detail is not as well demonstrated but determination of the presence, location, and size of renal tissue is possible. In no instance in this series did the ^{131}I-hippuran or ^{99m}Tc(Sn)-DTPA study provide better images of the renal parenchyma.

The use of ^{99m}Tc-DMSA in the evaluation of patients with pyelonephritis looks particularly interesting and work in this area is being carried out at the present time.

ACKNOWLEDGMENTS

The authors wish to express their thanks and appreciation to H. S. Winchell, Rose Ann Anderson, Alice Mercado, Linda Wuy, Dagmar Schmidt, Francine Hughes, and to the Nephrology Service, Pacific Presbyterian Medical Center (Allan M. Unger and W. D. Carey) for their advice, cooperation, and assistance. This work was supported in part by General Research Support Grant 5 501 RR05470-08.

REFERENCES

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

2. DAVIES ER, ROBERTS M, ROYLANCE J, et al: The renal scintigram in pyelonephritis. *Clin Radiol* 23: 370–376, 1972

3. WENZL JE, TAUXE WN, HUNT JC: A single injection technic for renal photoscanning with ortho-iodohippurate-I^{131}: A preliminary report. *Proc Staff Meet Mayo Clin* 38: 313–320, 1963

4. MCAFEE JG, WAGNER HN: Visualization of renal parenchyma by scintiscanning with Hg^{203} neohydrin. *Radiology* 75: 820–821, 1960

5. SODEE DB: A new scanning isotope, Mercury^{197}. A preliminary report. *J Nucl Med* 4: 335–344, 1963

6. REBA RC, HOSAIN F, WAGNER HN: Indium-113m diethylene-triaminepentaacetic acid (DTPA). A new radiopharmaceutical for study of the kidneys. *Radiology* 90: 147–149, 1968

7. AQUINO JA, CUNNINGHAM RM, YOUSSEF NR: ^{169}Yb-DTPA complex: another radiopharmaceutical for renal studies. *J Nucl Med* 10: 385–386, 1969

8. HAUSER W, ATKINS HL, NELSON KG, et al: Technetium-99m-DTPA: A new radiopharmaceutical for brain and kidney scanning. *Radiology* 94: 679–684, 1970

9. WINSTON MA, HALPERN SE, WEISS JS, et al: A critical evaluation of ^{99m}Tc-Fe-ascorbic acid complex as a renal scanning agent. *J Nucl Med* 12: 171–175, 1971

10. WINCHELL HS, LIN MS, SHIPLEY B, et al: Localization of polypeptide caseidin in the renal cortex: a new radioisotope carrier for renal studies. *J Nucl Med* 12: 678–682, 1971

11. HALPERN SE, TUBIS M, GOLDEN M, et al: ^{99m}TPAC, a new renal scanning agent. II. Evaluation in humans. *J Nucl Med* 13: 723–728, 1972

12. MCRAE J, BARRY AC, VALK PE: Renal scintigraphy using technetium stannous chloride gluconate. *Aust NZ J Med* 1: 291, 1971