Annals of Nuclear Medicine Vol. 5, No. 1, 29–34, 1991

Single photon emission computed tomography with Tc-99m-dimercaptosuccinic acid in patients with upper urinary tract infection and/or vesicoureteral reflux

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By means of Tc-99m dimercaptosuccinic acid (DMSA) scintigraphy, an established method for assessing renal cortical damage, we evaluated the pick-up rate for renal defects (scars) by single photon computed tomography (SPECT) and planar images of 10 normal volunteers, and 58 patients (70 scintigrams) with upper urinary tract infections, most of whom had a history of vesicoureteral reflux (VUR). The positive study rate for renal defects depended on the severity of VUR. The overall positive rates for renal cortical defects obtained by DMSA SPECT imaging and DMSA planar imaging were 60% and 43%, respectively, and the difference between these was significant ($p<0.005$). The mean absolute individual renal uptake (/injected dose) at 2 hours post-injection was decreased in kidneys with defects detected by SPECT alone. The positive study rate for intravenous urography (IVU) depended on the grade of VUR and was 15% overall.

DMSA SPECT imaging detects renal cortical defects at greater frequency than previously achieved.

Key words: Tc-99m dimercaptosuccinic acid (DMSA), single photon emission tomography (SPECT), urinary tract infection, vesicoureteral reflux, scarring

INTRODUCTION

Tc-99m dimercaptosuccinic acid (DMSA) has been established as an excellent renal cortical radioagent that provides high resolution images of renal anatomy as well as individual renal function.[1–7] A number of studies have shown that DMSA scintigraphy is very effective in detecting renal cortical defects (scars), particularly in patients with urinary tract infection (UTI) and/or vesicoureteral reflux (VUR).[8–13] These renal cortical defects have been recognized as predictors of the intrarenal reflux of infected urine.[14,15] DMSA scintigraphy has therefore been proposed as the initial method for disclosing and sizing cortical scars in UTI.[13,16] However, most of the reported analyses pertain to planar imaging.

This paper will compare and discuss the attributes of DMSA SPECT imaging in the detection of renal cortical defects.

MATERIALS AND METHODS

Materials

Between August, 1988 and December, 1989 108 DMSA studies (70 combined planar and SPECT studies and 38 planar alone) were conducted in 95 patients. All the patients had a clinical history of symptomatic UTI and/or VUR and were investigated by intravenous urography (IVU) and retrograde voiding cystourethrography (VCU) by a

Received December 5, 1990; revision accepted January 23, 1991.

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Table 1 Characteristics of the study population

	Normal	Patients		
		All	SPECT	Planar alone
Population	10	95	58	37
Male/Female	10/0	44/51	27/31	17/20
Age average	21 ys	14 ys	10 ys	17 ys
Range	20–23 ys	4 ms–65 ys	1 ys–48 ys	4 ms–65 ys
Treatment				
Medical	—	50	37	13
Surgical	—	45	21	24
UV-neostomy	—	36	18	18
TUR	—	6	3	3
Others	—	3	0	3
Scintigraphy	10	108	70	38

UV-neostomy: ureterovesical neostomy
TUR: transurethral resection

urologist. Forty-five of the 95 patients had already received surgical treatment to prevent urinary reflux and had been followed up over various periods. Another fifty patients were under medical treatment with antibiotics and/or anticholinergic agents for periods varying from a few months to more than 5 years. Clinical symptoms of UTI at the time of the scintigraphic examinations had subsided in all patients. The age of the patients ranged from 2 months to 64 years old (mean 14 yrs, median 7 yrs). In addition, 10 young adults who were normal volunteers were also investigated to assess normal cortical morphology in a planar and tomographic study. The characteristics of the study population are shown in Table 1.

Methods

Children who could not cooperate in the DMSA study were sedated. No other pre-treatment was indicated for individuals. Before injection, the syringe containing Tc-99m labeled DMSA was placed 30 cm from the collimator surface and counted for 10 sec in order to calibrate the device for renal uptake measurements. The patients were positioned supine on a bed beneath which the gamma camera (Toshiba GCA-602A, digital gamma camera) was located, and it was equipped with a low-energy high-resolution parallel-hole collimator. An intravenous bolus injection of 185 MBq of Tc-99m labeled DMSA for adults (scaled down to a minimum of 26 MBq for children) was given. Posterior planar images were obtained at precisely 2 hours after injection at a preset time of 5 minutes on a 512 by 512 matrix. Supplemental posterior oblique images were obtained in most patients. SPECT was started after the completion of the planar study. Each SPECT projection image was acquired on a 64 by 64 matrix for 20 sec at each of 60 positions over 360 degree rotation.

For reconstruction of tomograms, contiguous transaxial section images of every pixel width (5.4 mm thickness) were made by 3 point pre-smoothing and using a Shepp and Logan digital filter. Conventional

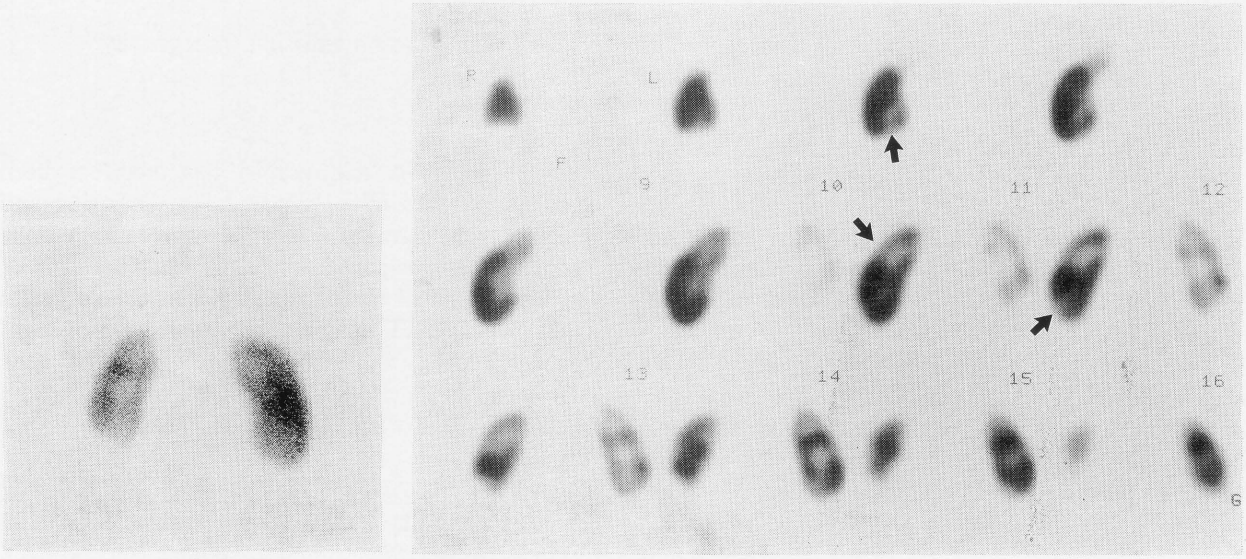


Fig. 1 Examples of Tc-99m DMSA scintigrams showing renal cortical defects in a patient with bilateral VUR (a 14-year-old boy). A: Posterior planar DMSA image, B: Coronal section SPECT image. Planar image (A) demonstrates multiple defects in the left kidney and equivocal decreased uptake in the upper and lower poles of the right kidney. Tomograms (B) show the presence of multiple defects (black arrows) in both kidneys.

transaxial and coronal images to the somatome axis and true coronal images to the visceral axis of the kidney after correction for renal axis rotation were generated. The three types of section images were displayed on a film for evaluation of renal morphology. The absolute individual renal uptake of DMSA per injected dose was calculated from posterior planar images by complete correction of all factors such as physical decay of Tc-99m from the time of injection to image data acquisition, and tissue attenuation of gamma energy emanating from Tc-99m DMSA in the kidney.[17]

All kidneys were classified by the grade of urinary reflux based on the findings at VCU. The grading of VUR was made by the degree of contrast material reflux into the lower and upper urinary tract according to the Dwoskin-Perlmutter classification.[18] It was found that in patients who had already received ureteral reconstruction and postsurgical medical treatment the grade of VUR varied at different follow-up examinations. Only the maximum reflux grade was employed for classification of the individual kidney. IVUs and DMSA scintigrams closest in time, performed within one month, were compared for cortical anatomical identification. The signs of scarring on the IVU were calyceal clubbing and deformity in association with parenchymal thinning. A wedge-shaped or band-like decreased uptake in renal parenchyma on the planar DMSA image and decreased uptake across the renal parenchyma on SPECT DMSA images were criteria of cortical defects by scintigraphy (Fig. 1). Normal anatomical decreased uptake that was revealed between Bertin's columns on SPECT was excluded from abnormal findings. These findings were retrospectively reviewed and used in the statistical analysis.

Statistical methods

Chi-square test was used to determine if a significant difference in the number of renal cortical defects existed between the SPECT imaging, planar imaging and IVU. There was a normal distribution of absolute individual DMSA uptake within each group, and therefore Student's t-test was applied to judge significance.

RESULTS

Planar versus SPECT

The positive study rate for renal cortical defects was compared in planar and SPECT images in the 20 kidneys of 10 normal volunteers and 134 kidneys in 70 scintigrams of 58 patients. In volunteers, planar images were all normal and all except one were normal by SPECT. The one abnormal left kidney showed decreased uptake in the upper pole. He did not have a clinical history of pyelonephritis or hypertension; no further investigation was conducted. In patients, the positive rate of DMSA scintigraphy for renal defects was enhanced by adding SPECT images in all groups: no VUR, 23% planar and 50% SPECT; grade I, 35% planar and 50% SPECT; grade IIa, 28% planar and 50% SPECT; grade IIb, 55% planar and 73% SPECT; grade III, 64% planar and 71% SPECT; grade IV, 85% planar and 100% SPECT. The greatest percentage of improvement detected by SPECT was in mild grades of reflux (Table 2). SPECT missed a small cortical defect in only one kidney, and this was picked up on the planar image in the lower margin of the left kidney in an infant. Overall, the positive study rate for SPECT DMSA imaging was 61% compared to 43% by planar imaging, which is statistically significant ($p<0.005$).

Table 2 Comparison of positive study rate for the detection of renal cortical defects by planar and SPECT imagings

Scintigraphic evaluation	Normal volunteers (n=20)	Grading of VUR					
		No VUR (n=22)	I (n=26)	IIa (n=36)	IIb (n=22)	III (n=14)	IV (n=14)
Planar (+)	—	23%	35%	25%	55%	64%	86%
SPECT (+)		(5)	(9)	(9)	(12)	(9)	(12)
Planar (−)	5%	27%	15%	22%	18%	7%	14%
SPECT (+)	(1)	(6)	(4)	(8)	(4)	(1)	(2)
Planar (+)	—	—	—	3%	—	—	—
SPECT (−)				(1)			
Total	5%	50%	50%	50%	73%	71%	100%
	(1)	(11)	(13)	(18)	(16)	(10)	(14)

The numbers in parenthesis indicate the number of kidneys.
The positive study rate for planar imaging in patients is 43% (57/134).
The positive study rate for SPECT imaging in patients is 60% (81/134).

The absolute individual renal uptake in patients is plotted in Fig. 2. The mean absolute individual renal uptake (±SD) in the kidneys with no defects, with defects detected by both planar and SPECT imaging and with defects detected by SPECT alone were 0.204±0.081 (n=46), 0.167±0.061 (n=46) and 0.185±0.048 (n=23), respectively. The first two mean values were statistically significant ($p<0.005$), whereas the last two mean values were not. On the other hand, the uptake in normal volunteers was 0.181±0.025.

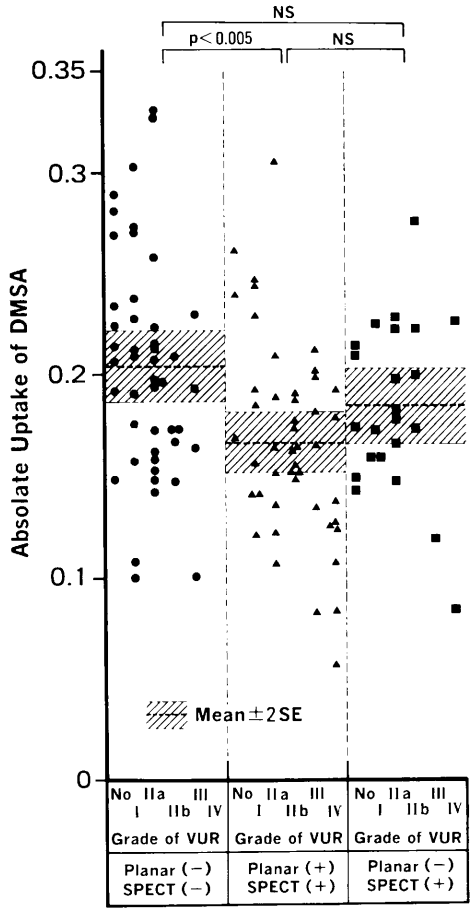


Fig. 2 The individual absolute renal uptake of Tc-99m-DMSA in the kidney with or without defects on planar and/or SPECT scintigraphy.

Intravenous urogram versus planar Tc-99m DMSA image

We also compared the positive study rate of DMSA planar imaging with IVU. The positive study rate for renal scars on IVU depended on the grade of VUR and increased proportionately with the reflux grade. The lowest positive rate was 0% (0/35) in the group with no VUR and the highest was 44% (8/18) in the group with grade IV reflux. The overall positive rate of the IVU for scarred kidneys was 15% (27/176). In contrast, planar DMSA scintigraphy showed higher positive rates in every group with reflux than the IVU. The positive study rate of planar DMSA imaging was almost the same in groups with no VUR, and grades I and IIa. It ranged from 20% to 29%. In groups with advanced reflux grades IIb, III and IV, cortical defects were more frequently disclosed, varying from 59% to 77%. The overall positive study rate of planar DMSA scintigraphy was 41% (74/181) which was significantly greater than the IVU ($p<0.001$). These results are detailed in Table 3.

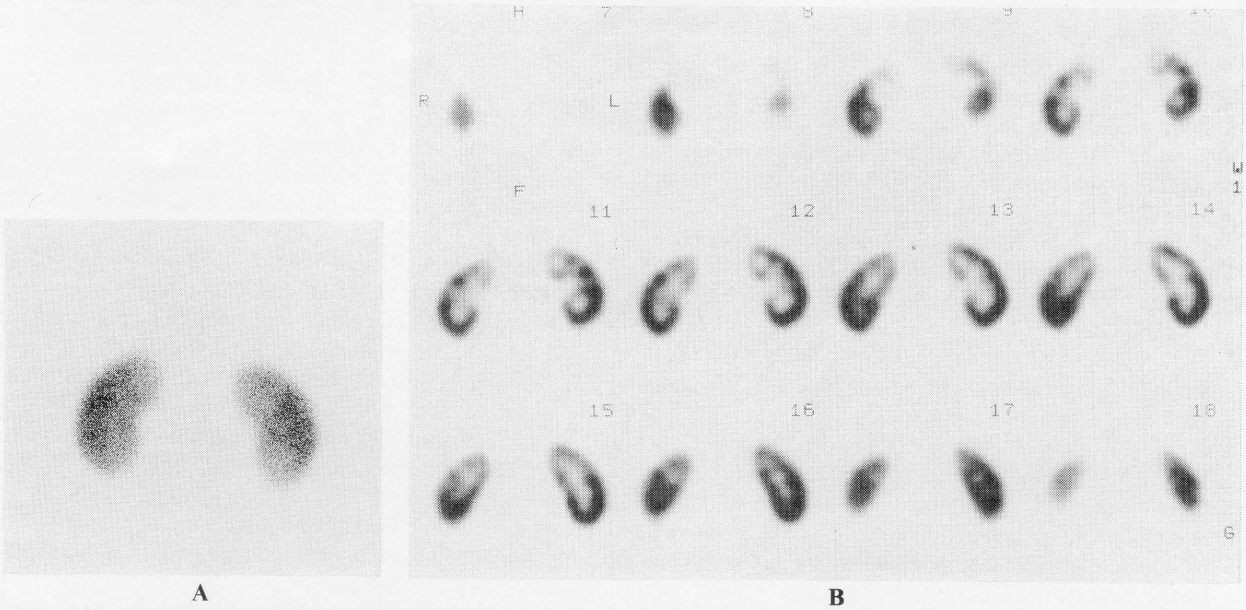
DISCUSSION

Of the three diagnostic methods under study, viz., Tc-99m DMSA SPECT imaging, Tc-99m DMSA planar imaging and IVU, the first yielded the highest positive study rate in the detection of renal cortical defects. The positive study rate of 43% for renal cortical defects by planar DMSA scintigrams was similar to the previous series (24–51%),[8,12,13] but our overall figure of 15% for the IVU is lower than any other reported series (32–37%). This may be due to differences in the severity of VUR in the study population. Although the IVU did show the lowest positive study rate in the detection of renal scars, it still serves as a baseline study to evaluate anatomical details of the calyces and ureters. The addition of SPECT enhanced overall detection of the cortical defects from 43% in planar imaging to 60% by SPECT. There have been no previously reported studies which compared the attributes of DMSA SPECT imaging to planar for the detection of renal

Table 3 Comparison of positive study rate for the detection of renal cortical defects by intravenous urography (IVU) and planar DMSA imaging

Methods	Grading of VUR						
	No VUR	I	IIa	IIb	III	IV	Overall
IVU	0% (0/35)	7% (2/28)	12% (5/43)	18% (6/34)	33% (6/18)	44% (8/18)	15% (27/176)
Planar DMSA	20% (7/35)	29% (8/28)	23% (10/44)	59% (20/34)	67% (12/18)	77% (17/22)	41% (74/181)

The numbers in parenthesis indicate the number of kidneys.



A B

Fig. 3 Tc-99m DMSA SPECT images in a normal volunteer. SPECT image shows stripes of increased (corresponding to the Bertin's columns) and decreased (corresponding to the pyramids) uptake in the renal cortex, paticularly in the mid-portion of the kidney.

cortical defects in patients with UTI and/or VUR.

The renal parenchymal defects demonstrated by DMSA scintigraphy, however, are not pathognomonic for renal scars. They are observed in many renal diseases which induce loss of functioning mass such cysts, tumors, infarction, etc. In addition, we must keep in mind that false positive defects resulting from the application of SPECT are not negligible. The renal axis rotation and intra-parenchymal regional distribution of functioning nephrons in the Bertin's columns and the pyramids, revealing stripes of increased and decreased uptake (Fig. 3), also may produce false positive results. Cortical defects, therefore, must be interpreted in the clinical and anatomical contexts.[2–4] In the clinical study, it is difficult to calculate the true sensitivity and specificity of Tc-99m DMSA scintigraphy for renal cortical scars, because there are few correlations with pathological specimens, the gold standard. The results of an experimental study using piglets[19,20] also indicate that there was no false positive in planar DMSA scintigraphy, although small infection scars tended to be missed by planar imaging. The two reports seem to clearly indicate the clinical usefulness of DMSA SPECT imaging in the detection of infection scars, because the application of SPECT might improve anatomical resolution for such small defects in infected kidney.

Although DMSA scintigraphy may have limitations in tissue characterization of the parenchymal defects and SPECT imaging may produce some false positive results, the scarred kidneys that were detected only by DMSA SPECT tended to have decreased renal uptake. This suggests that the scarred kidneys disclosed only by SPECT have some loss of functioning mass, but it is not statistically significant, and is due to small defects which are overshadowed by radioactivity in and around the kidney. The clinical significance of these cortical defects which are detected only by SPECT and do not result in significant loss of cortical function remain to be determined in a further study. Calculation of the absolute individual DMSA uptake is helpful for quantitative estimation of the functioning mass of the kidney.

The renal defects demonstrated by DMSA scintigraphy clearly indicate recent and/or past upper urinary tract infection. DMSA scintigraphy is therefore proposed as a new highly reliable standard for the investigation of renal scarring in young children with UTIs.[21] The only limitations to DMSA SPECT are the somewhat longer imaging time compared to planar, and the necessity of using sedation in younger children, but it is more sensitive than either IVU or DMSA planar imaging. The clinical facility of DMSA SPECT imaging in younger children should be further discussed and established in the therapy and longitudinal follow-up of these patients.

REFERENCES

1. Lin TH, Khentigan A, Winchell HS: A ^{99m}Tc-chelate substitute for organo-radiomercurial renal agents. *J Nucl Med* 15: 34–35, 1974
2. Handmaker H, Young BW, Lowenstein JW: Clinical experience with ^{99m}Tc-DMSA (Dimercaptosuccinic acid), a new renal imaging agent. *J Nucl Med* 16:

28–32, 1975
3. Bingham JB, Maisey MN: An evaluation of the use of ^{99m}Tc-dimercapto-succinic acid (DMSA) as a static renal imaging agent. *Brit J Rad* 51: 599–607, 1978
4. Daly MJ, Henry RE: Defining renal anatomy and function with ^{99m}Technetium dimercaptossuccinic acid: Clinical and renographic correlation. *J Urol* 126: 5–9, 1981
5. Kawamura J, Hosokawa S, Yoshida O, et al: Validity of ^{99m}Tc-dimercapto-succinic acid renal uptake for an assessment of individual kidney function. *J Urol* 110: 305–309, 1978
6. Taylor A, Jr: Quantitation of renal function with static imaging agents. *Semin Nucl Med* 12: 330–344, 1982
7. Gordon I, Evans K, Peters AM, et al: The quantitation of ^{99m}Tc-DMSA in paediatrics. *Nucl Med Comm* 8: 661–670, 1987
8. Merrick MV, Uttley WS, Wild SR: The detection of pyelonephritic scarring in children by radioisotope imaging. *Brit J Radiol* 53: 544–556, 1980
9. Whitaker RH, Sherwood T: Another look at diagnostic pathways in children with urinary tract infection. *Brit Med J* 288: 839–841, 1986.
10. Gordon I. Use of Tc-99m DMSA and Tc-99m DTPA in reflux. *Semin Urol* 9: 99–109, 1986
11. Gordon I: Indications for ^{99m}Technetium dimercapto-succinic acid scan in children. *J Urol* 137: 464–467, 1987
12. Monsour M, Azmy AF, MacKenzie JR: Renal scarring to vesioureteric reflux. Critical assessment and new grading. *Brit J Urol* 60: 320–324, 1987
13. Verber IG, Studley MR, Meller ST: ^{99m}Tc dimercapto-succinic acid (DMSA) scan as first investigation of urinary tract infection. *Arch Dis Child* 63: 1320–1325, 1988
14. MacGregor M: Pyelonephritis Lenta. Consideration of childhood urinary infection as forerunner of renal insufficiency in later life. *Arch Dis Child* 45: 159–172, 1970
15. Ransley MA, Risdon RA: Reflux and renal scarring. *Brit J Rad Suppl* 14: 1–35, 1978
16. Conway JJ: The role of scintigraphy in urinary tract infection. *Semin Nucl Med* 18: 308–319, 1988
17. Itoh K, Asano Y, Kato C, et al: Quantitation of absolute and relative renal uptake using ^{99m}Tc-DMSA: sequential change in time and correlation to ^{99m}Tc-DTPA uptake. *Jpn J Nucl Med* 27: 237–242, 1990
18. Dwoskin JY, Perlmutter AD: Vesicoureteral reflux in children: A computerized review. *J Urol* 109: 888–890, 1973
19. Rushton HG, Majd M, Chandra R, Yim D: Evaluation of ^{99m}Technetium-dimercapto-succinic acid renal scans in experimental acute pyelonephritis in piglets. *J Urol* 140: 1169–1174, 1988
20. Parkhouse HF, Godley ML, Cooper J, et al: Renal imaging with ^{99m}Tc-labelled DMSA in the detection of acute pyelonephritis: an experimental study in the pig. *Nucl Med Comm* 10: 63–70, 1989
21. MacKenzie JR: DMSA-the new "gold standard". *Nucl Med Comm* 11 (editorial): 725–726, 1990