Measurement of renal function by calculation of fractional uptake of technetium–99m dimercaptosuccinic acid

Slobodanka Lj. Beatović, Emilija D. Jakšić, Ruben S. Han
Institute of Nuclear Medicine, Clinical Center of Serbia, Belgrade

Abstract

BACKGROUND: The purpose of this study was to set up normal values of the fractional uptake (FU) of technetium-99m dimercaptosuccinic acid in adults and in the pediatric population, as well as to evaluate the validity of this parameter at different levels of renal function.

MATERIAL AND METHODS: A total of 86 subjects was divided into seven groups. In group A there were 23 potential kidney donors and in group B, 18 children in remission after a first urinary tract infection. Another three groups consisted of patients with diabetes i.e. group C, seven patients with normal values of albuminuria, group D, 16 patients with microalbuminuria and group E, five patients with macroalbuminuria. In group F, there were ten patients with a well-functioning transplanted kidney and in group G, seven patients with suspected acute rejection. The procedure began with the quantification of the doses of 99mTc-DMSA to be injected and the measurement of the empty syringe lying on the gamma camera collimator. Thereafter, four planar views of the kidneys were acquired three hours after the injection. The counts from the posterior and anterior views were subtracted for background and corrected for radioactive decay time and patient thickness. The FU was calculated by the geometric mean of counts per second from the posterior and anterior view. It was expressed as a fraction of the injected dose.

RESULTS: The mean values of FU in healthy adults were 0.227 ± 0.077 for one kidney and 0.454 ± 0.146 for both kidneys. The mean values of FU for the left and right kidney were 0.225 ± 0.071 and 0.229 ± 0.079, respectively. In children, the mean values were 0.220 ± 0.092 for one kidney and 0.432 ± 0.094 for both kidneys. The highest values of FU of 0.322 ± 0.078 (0.644 ± 0.138 for both kidneys) were measured in group C. In group D, FU was 0.185 ± 0.065 (0.361 ± 0.125 for both kidneys) and in group E 0.082 ± 0.040 (0.163 ± 0.080 total). In patients with a transplanted kidney, fractional uptake was 0.162 ± 0.039 in group F and 0.065 ± 0.021 in group G. There was no significant difference in the values of FU between healthy adults and children. The uptake in group C was 41% higher than in group A and the difference was statistically significant. In groups D and E, the uptake was significantly lower than in A. In both groups of patients with transplanted kidneys, the uptake was significantly lower than in control group. The correlation between FU and biochemical parameters of renal function [blood urea nitrogen (BUN), serum creatinine (Cr) and creatinine clearance (C_{Cr})] was significant: FU/BUN $r = -0.86$; FU/Cr $r = -0.77$; FU/C_{Cr} $r = 0.60$.

CONCLUSION: Fractional uptake of 99mTc-DMSA could serve as a sensitive parameter of renal function. The mean values of FU in adults were 0.454 and in children 0.432. There was no significant difference between values for the left and right kidney. In diabetes mellitus, fractional uptake correlated well with the degree of diabetic nephropathy. In patients with a well-functioning transplant, the uptake was slightly reduced. Low values of fractional uptake in acute rejection were related to lesions in kidney blood vessels and in tubular cells.

Key words: kidney function, renal scintigraphy, dimercapto-succinic acid, fractional kidney uptake, transplanted kidney, diabetic nephropathy

Correspondence to: Slobodanka Lj. Beatović
Institute of Nuclear Medicine CCS
Višegradska 26, 11000 Belgrade
Tel: (+381 11) 423221, fax: (+381 11) 2441600
e-mail: nuklearna@beotel.yu, sbeat@eunet.yu

Introduction

Labeled dimercaptosuccinic acid (DMSA) has been in use for more then thirty years for imaging the renal parenchyma, renal anatomy, kidney size, position and shape. It has become the radiopharmaceutical of choice for static renal scintigraphy and the estimation of functioning renal mass, due to its particular uptake in the renal cortex [1].

The uptake of DMSA in the kidney is the result of the complex interaction of glomerular filtration, peritubular uptake and tubular secretion. This diverse process is sometimes called tubular fixation. The extraction of DMSA from the peritubular extracellular fluid into the tubular cells remains, however, the main route of renal handling [2]. Despite the slow transfer of DMSA from the blood to the kidney, about 50% of the injected activity is taken up within one hour after injection.

Relative right to left kidney uptake of DMSA is a very good indicator of differential function of proximal part of the tubuli and loops of Henley. A more comprehensive renal evaluation, including individual kidney cortical function can be obtained by calculation of fractional uptake of DMSA in the kidneys [3]. Quantification of kidney uptake is applied in the measurement of residual renal function, for serial measurements of renal function when some intervention is planned or to monitor renal function in order to detect progressive loss of function [4].

The purpose of this study was to set up the normal values of fractional uptake in adults and in the pediatric population, in order to use this parameter routinely in assessing renal function. Furthermore, the sensitivity of FU at different levels of renal function impairment was evaluated in patients with native kidneys and those with kidney transplants.

Material and methods

The investigation was carried out in 86 subjects: 68 adults (33 males and 35 females, mean age 39.6 ± 10.5) years and 18 children (6 boys and 12 girls, mean age 10.1 ± 2.5 years). According to the clinical diagnosis and the degree of renal function impairment, they were divided into seven groups. The first two groups consisted of healthy individuals. The population of potential kidney donors was used to establish the group of healthy adults. The selection for the control group of children was made among pediatric patients in remission after a first urinary tract infection. DMSA renal scans of these individuals were made and two independent observers classified them as normal and abnormal. 23 normal scintigrams of adults were used for group A and 18 normal scintigrams of children were selected for group B. All patients of these two groups underwent ultrasound examination and no pathological finding was revealed.

In another three groups where patients had diabetes: group C consisted of seven patients with normal values of albuminuria (less than 7 mg/day), group D of 16 patients with microalbuminuria and group E of 5 patients with clinically detectable proteinuria (more than 500 mg/day). The two last groups consisted of patients with transplanted kidney: group F of 10 patients with well-functioning transplant and group G of 7 patients with suspected acute rejection.

In all patients, blood urea nitrogen (BUN), serum creatinine (Cr) and creatinine clearance (C_{Cr}) were measured 24 hours before scintigraphy.

For the estimation of creatinine clearance, urine was collected over 24 hours. The following equation was used:

$$\textit{Creatinine cearance } [ml/min] = \frac{U_{cr} [mg\%] \times Q [ml]}{P_{cr} [mg\%] \times 1440 [min]}$$

where:

U_{cr} — urinary creatinine concentration,

Q — volume of urine in 24 h,

P_{cr} — serum creatinine concentration.

Values of creatinine clearance in children were normalized to 1.73 m^2 of body surface. Patients were hydrated prior the examination with 10 ml of fluid per kilogram of body weight.

99mTc-DMSA preparation: DMSA was provided in a commercial kit form (Institute for Nuclear Science "Vinča", Belgrade, Serbia) and stored at 4°C. Each vial contained 2 mg DMSA and 0.8 mg $SnCl_2$ in a lyophilized form. The 99mTc generator (Institute for Nuclear Science "Vinča", Belgrade) was eluted into three aliquots and 740 MBq from the second one was added to the kit. The total volume of reconstituted 99mTc-DMSA was made up to 5 ml with normal saline. The 99mTc-DMSA was kept at room temperature and injected between 30 and 60 min after preparation. The standard dose for a 70-kg adult was 100 MBq. In children, the doses where adjusted to the age and weight, according to the recommendations of Pediatric Task Group of EANM. The minimal activity injected was 20 MBq.

Data acquisition: Acquisition was performed on a single-headed gamma camera Orbiter ZLC 3700 (Siemens, Erlangen, Germany), equipped with low-energy, high resolution collimator. The dose syringe was counted on gamma camera face for one minute before and after the injection. The exact times when countings were performed were noted. In all patients, extravasations of the tracer at the injection site were excluded. Static renal scintigraphy was done 3 hours after the injection. With the patient lying supine on the bed, four images were taken: posterior, anterior, left lateral, right lateral. Lateral views were recorded for the measurement of total body-part thickness. Images were collected in a 256 × 256 resolution matrix with 600 kcounts acquired.

Background correction: C-shaped regions of interest, outlined above the superior, lateral and inferior aspects of the kidney were used for the subtraction of background.

Calculation of 99mTc-DMSA fractional uptake: Fractional uptake was calculated by "conjugate-view method", which uses the geometric mean of counting rates from the posterior and the anterior view, as well as the patient's total body-part thickness. Physical decay of 99mTc and soft tissue attenuation were also taken into account. The following formula was used:

$$FU = \frac{1}{D_1 - D_2} \left\{ (C_1 \times C_2) \times e^{\frac{T \times \ln 2}{\tau}} \right\}^{\frac{1}{2}} \times e^{\mu \times \frac{L}{2}}$$

where:

D_1 — activity of syringe + dose (counts/second),

D_2 — activity of empty syringe (counts/second),

$D = (D_1 - D_2)$ — injected activity (counts/second),

C_1 — background subtracted counts per second from the posterior view of kidney,

C_2 — background subtracted counts per second from the anterior view of kidney,

T — time interval (scan time minus injection time),
τ — half-life of 99mTc,
μ — linear attenuation coefficient of 99mTc,
L — total body-part thickness

Attenuation coefficient for 99mTc was measured using Perspex phantom and found to be 0.122 cm^{-1}.

FU was expressed as a fraction of the injected activity.

For statistical analysis of the obtained data, the usual methods of descriptive and inferential statistics were used. Fractional uptake was reported as mean ($\pm$ SD) values. The differences between the renal uptake rates in different groups of patients were evaluated using Student's t-test. P-values less than 0.05 were considered statistically significant. In addition, linear regression analysis was performed, by means of regression equation and correlation coefficient calculation.

Results

Figures 1–3 display absolute mean kidney uptakes in all 86 subjects (157 kidney units). The mean values of FU in healthy adults were 0.227 $\pm$ 0.077 for one kidney and 0.454 $\pm$ 0.146 for both kidneys. For the left kidney, the mean values were 0.225 $\pm$ 0.071 and for the right kidney 0.229 $\pm$ 0.079. In children, the mean values were 0.220 $\pm$ 0.092 for one kidney and 0.432 $\pm$ 0.094 for both kidneys. There was no significant difference in the values of fractional uptake between healthy adults and children (p > 0.05). The highest values of FU of 0.322 $\pm$ 0.078 (0.644 $\pm$ 0.138 global) were measured in diabetic patients without albuminuria (C). In group D, the mean values of FU were 0.185 $\pm$ 0.065 (0.361 $\pm$ 0.125 global) and in group E 0.082 $\pm$ 0.040 (0.163 $\pm$ 0.080 global). The uptake in group C was 41% higher than in group A, 78% higher than in D and four times higher than in E. In group D, FU was 18% lower than in A. Group E showed 64% lower values than in A and 55% lower values than in D. In patients with well-functioning transplants, the uptake was 0.162 $\pm$ 0.039. These values were 28% lower than in group A. The lowest FU values of 0.065 $\pm$ 0.021 were measured in group of patients with acute rejection (G). The values in this group were 71% lower than in group A and 60% lower than in group F. There was no overlap between groups F and G: the highest value in group G of 0.095 was lower than the lowest values in group F of 0.110.

The correlation between fractional uptake and biochemical parameters of renal function was significant. Negative correlation was obtained between blood urea nitrogen and uptake of 99mTc-DMSA (r = –0.86), as well as between serum creatinine and uptake of 99mTc-DMSA (r = –0.77). The correlation between creatinine clearance and FU was positive (r = 0.60).

Discussion

There were two control groups in our study. We used the population of potential kidney donors and those with normal values of relevant biochemical tests and normal findings on renal ultrasound and DMSA scintigraphy were selected for the control group of adults. Similarly, the pediatric patients in remission after a first urinary tract infection with normal ultrasound and DMSA renal scintigrams made a control group for the child population.
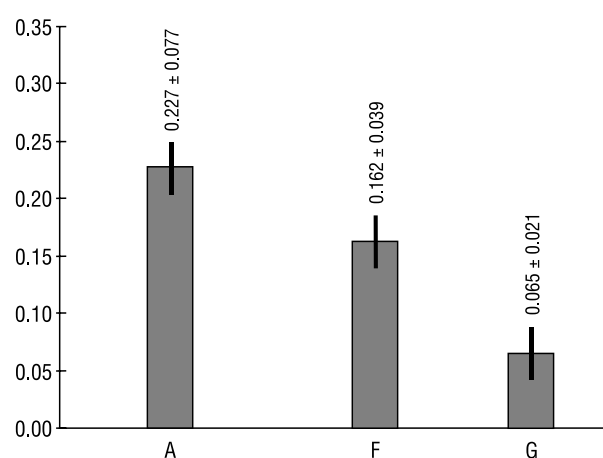
We measured kidney uptake of DMSA three hours after the injection, due to the heavy workload in our very busy department.
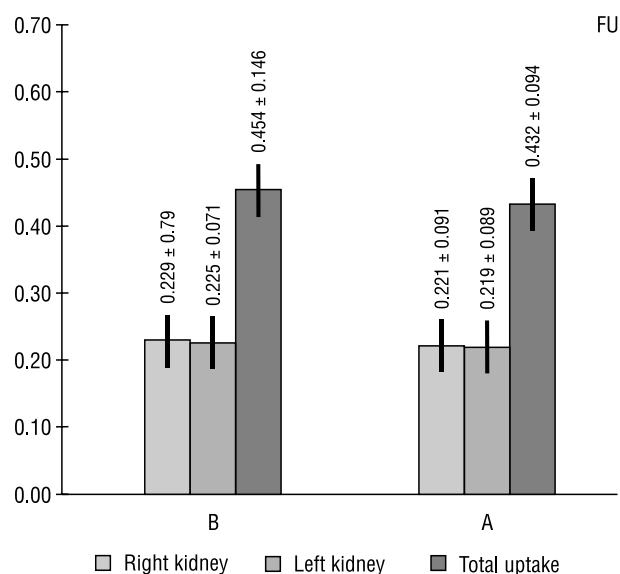
Figure 1. Tc-99m DMSA fractional uptake of left kidney, right kidney and total in healthy adults (A) and healthy children (B).
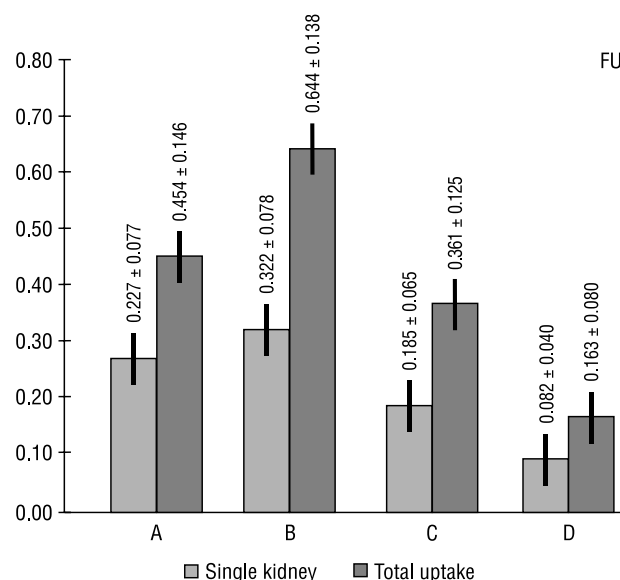
Figure 2. Tc-99m DMSA uptake of one kidney and total uptake in patients with diabetes mellitus: comparison with control group.

Figure 3. Tc-99m DMSA uptake in groups of patients with transplanted kidney: comparison with one kidney uptake in control group.

Although the uptake increases continuously after three hours and reaches plateau between six and eight hours, the difference between three and six hours uptake is just about 4% [5].

The handling of DMSA by the kidneys depends on a functioning renal cortical mass and cortical perfusion. Thus, renal cortical uptake of DMSA, expressed as a fraction of the administered dose reflects individual renal function [6].

Among several methods that have been established for kidney uptake quantification, the "conjugate view" represents plausible compromise between simplicity and accuracy [7]. This method is little more elaborate due to additional anterior view of kidneys, but should be applied when the difference in radiation attenuation is expected, especially in cases with an anatomical abnormalities of the kidney.

The values of FU obtained in our study were in accordance with the results of other authors. Murase et al. who also applied the conjugate view method [8] measured one kidney uptake with a mean value of 0.228 ± 0.074. The results of Zananiri et al. [9] of 0.254 ± 0.089 were higher in comparison with ours, but the method applied took kidney thickness into account and was much more elaborate. Gordon et al. [10] measured six hour DMSA uptake in healthy children and obtained the values of 0.441 for both kidneys. Tsukamoto et al. [11] reported normal values of fractional uptake in a pediatric population: 0.407, 0.202 and 0.204 for both kidneys, right and left kidneys, respectively. The results of Gordon et al. [10] and Tsukamoto et al. [11] were comparable with our values of three hour uptake in a group of healthy children.

In patients with diabetes, absolute uptake was in a significant correlation with the degree of diabetic nephropathy. Diabetic patients with normal values of albuminuria showed significantly higher FU in comparison with the control group. This could be a result of renal vasodilatation and subsequent hyperperfusion, due to neurohumoral changes that occur in diabetes (decreased plasma rennin activity and angiotensin II levels, diminished response to angiotensin II and norepinefrin, increased production of prostaglandins and glucagon and extracellular volume expansion) [12]. In patients with microalbuminuria, values of FU were significantly lower than in the control group. The deterioration of FU is probably due to the narrowing of the afferent and efferent arterioles. In patients with macroalbuminuria, extensive tubulointerstitial changes (tubular atrophy, interstitial fibrosis) are responsible for progressive decrease of renal DMSA uptake.

In patients a with well-functioning transplanted kidney, the uptake was slightly reduced, probably due to an acute tubular lesion, which is common in the early post transplantation period, particularly in cadaver kidney grafts. The patients with acute rejection of transplanted kidney showed low values of fractional uptake. This finding is probably caused by the extensive pathological changes of kidney blood vessels, and tubular cells [13].

The results of our study confirmed that the estimation of the fractional uptake of 99mTc-DMSA gives additional quantitative information on cortical and renal mass function. Besides its well-established usefulness in follow-up of children at risk for progressive renal damage and in the measurement of renal function prior an intervention, FU estimation could be performed as a part of a majority of 99mTc-DMSA studies. The individual and global specific uptake of 99mTc-DMSA could also help to assess renal function impairment in diabetes mellitus, as well as in kidneys at early post-transplantation period.

References

1. Eshima D, Fritzberg AR. Radiopharmaceuticals for renal imaging. In Nucl Med Ed. Henkin R.E. Mosby-Year Book inc. St. Louis Missouri 1996; 1055–1064.
2. de Lange MJ, Piers DA, Kosterink JGW et al. Renal handling of Technetium-99m DMSA: evidence for glomerular filtration and peritubular uptake. J Nucl Med 1989; 30: 1219–1223.
3. Taylor A Jr. Radionuclide evaluation of renal function. Crit Rev Diagn Imaging 1991; 32: 1–36.
4. Groshar D, Embon OM, Alex F, Front D. Renal function and technetium-99m-dimercaptosuccinic acid uptake in single kidneys: the value of in vivo SPECT quantitation. J Nucl Med 1991; 32: 766–768.
5. Flower AM, Meller ST, Chittenden SJ, Fielding SL, Evans K, Gordon I. Absolute Tc-99m DMSA renal uptake in children: Optimum time to scan. Nucl Med Commun 1995; 16: 572–574.
6. Kawamura J, Hosokawa S, Yoshida O, Fujita T, Ishii Y, Torizuka K. Validity of Tc-99m dimercaptosuccinic acid renal uptake for an assessment of individual kidney function. J Urol 1978; 119: 305–309.
7. Itoh K, Yamashita T, Tsukamoto E, Nonomura K, Furudate M, Koyanagi T. Quantitative evaluation of renal parenchymal damage by Tc-99m DMSA planar and SPECT scintigraphy. Ann Nucl Med 1995; 9 : 23–28.
8. Murase K, Tanada S, Ishine M, Yokoyama M, Hamamoto K. Methods for measuring the renal uptake od Tc-99m-dimercaptposuccinic acid (DMSA): a comparative study. Eur J Nucl Med 1990;16: 725–731.
9. Zananiri MC, Jarrit PH, Sarfarazi M, Ell PJ. Relative and absolute 99mTc-DMSA uptake measurements in normal and obstructed kidneys. Nucl Med Commun 1987; 8: 869–880.
10. Gordon I, Evans K, Peters AM et al. The quantitation of Tc-99m DMSA in paediatrics. Nucl Med Commun 1987; 8: 661–670.
11. Tsukamoto E, Itoh K, Katoh C et al. Validity of 99mTc-DMSA renal uptake by planar posterior-view method in children. Ann Nucl Med 1999; 13: 383–387.
12. Rose BD, Jacobs JB. Nephrotic syndrome and glomerulonephritis. In: Pathophysiology of Renal Disease. Ed. Rose B.D. McGraw-Hill Book Company 1987: 179–297.
13. Coe FL. Clinical and laboratory assessment of the patient with renal disease. in The Kidney. Ed. Brener BM. and Rector FC. WB. Saunders Company, Philadelphia 1986: 703–732.