Relative ^{99m}Tc-MAG3 Renal Uptake: Reproducibility and Accuracy

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The aim of this study was to estimate the reproducibility and accuracy of ^{99m}Tc-mercaptoacetyltriglycine (MAG3) relative percentage uptake. **Methods:** Reproducibility was evaluated on healthy volunteers who were submitted twice to a ^{99m}Tc-MAG3 renographic study, which used different uptake algorithms, different background corrections and different time intervals. Accuracy was evaluated in a group of patients with symmetrical or asymmetrical relative renal function, who underwent both ^{99m}Tc-dimercaptosuccinic acid (DMSA) and ^{99m}Tc-MAG3 studies, using the DMSA relative percentage uptake as a reference. **Results and Conclusion:** The methods that combined the best reproducibility and accuracy for estimating ^{99m}Tc-MAG3 left-to-right uptake ratio were the integral method, with subrenal or perirenal background correction, and the Patlak-Rutland plot. The use of the integral method without background correction introduced a systematic bias, whereas the slope method resulted in high variability. Therefore these methods cannot be recommended.

Key Words: ^{99m}Tc-mercaptoacetyltriglycine; ^{99m}Tc-dimercaptosuccinic acid; relative renal uptake; reproducibility; accuracy

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Measurement of individual kidney uptake is the main parameter provided by the renogram. Several methods allowing the measurement of absolute individual kidney function have been published. All, however, necessitate an estimation of net renal counts, including correction for tissue absorption, and the expression of the results in milliliters per minute using accurate calibration of heart curves or adequate tables converting an uptake ratio into a clearance value (*1*).

Measurement of relative function is easier and can eventually be combined with a plasma sample method to derive an individual function expressed in milliliters per minute per kidney. The integral and slope methods have each been used widely for the estimation of relative function (*2–9*). The respective accuracy and reproducibility of these methods remain to be determined.

A consensus on renal clearance suggests that "the preferred technique for the measurement of individual renal function utilizes camera counts between 1 and 2 or 2.5 min" (*10*). No consensus could be reached as to whether background correction should be used or which type of background should be applied.

The aim of this study was, first, with healthy volunteers and two renographic studies using ^{99m}Tc-mercaptoacetyltriglycine (MAG3), to estimate the reproducibility of the relative percentage uptake using different uptake algorithms, background corrections and time intervals. Second, the aim was to estimate the accuracy of these methods in a group of patients who underwent both ^{99m}Tc-dimercaptosuccinic acid (DMSA) and ^{99m}Tc-MAG3 studies, using the DMSA relative percentage uptake as a reference.

MATERIALS AND METHODS

Reproducibility

Thirteen healthy volunteers (age range 21–30 y) were enrolled in this study. They had no history of serious medical problems, and blood pressures were normal. None was receiving any medication. The study was approved by the ethical committee of Akademisch Ziekenhuis.

The volunteers had light breakfasts early in the morning and were hydrated with standard oral preparation of approximately 0.5 L of any fluid. Tracer injection was performed at around 8 AM, and the procedure was repeated 1 wk later under the same conditions.

A commercial preparation of ^{99m}Tc-MAG3 (185 MBq) was used in accordance with the recommendations of the manufacturer (Mallinckrodt, Petten, The Netherlands). All doses used during the study were issued from the same batch.

The patient was placed in supine position above the gamma camera, and the tracer was injected intravenously and rapidly flushed with saline. After a 20-min acquisition using 20-s frames, the patient's arm was positioned above the gamma camera to detect any vascular escape of the tracer at the time of the injection. In no case could significant local uptake be detected. Quadrangular regions of interest (ROIs) were drawn manually over each kidney.

Several uptake algorithms, background corrections and time intervals were used in various combinations. These combinations are presented in Table 1.

Algorithms. The integral method measured renal counts during a predetermined time interval in the early phase of the renogram. In the slope method, the first derivative of the early part of the renogram was divided by the corresponding heart counts obtained from a large quadrangular area centered on the highest cardiac activity.

Background Correction. Three types of background correction were used: (a) no correction at all, (b) quadrangular perirenal area

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TABLE 1
Reproducibility in Healthy Volunteers of Relative Percentage Uptake (SD of Differences Between First and Second Measurements in Right Kidney)

Selection of points	Integral 1	2	3	Slope 4	5	6	Patlak-Rutland algorithm 7
A	1.3	1.7	1.5	4.1	3.4	7.5	5.3
B	1.3	1.7	1.5	4.4	4.1	11.5	2.8
C	1.3	1.7	1.5	5.8	5.2	8.2	3.7

Integral = summing up number of counts between two given points of renogram (1 = no background correction; 2 = background correction using rectangular perirenal area; 3 = background correction using subrenal area); Slope = first derivative of early part of renogram divided by corresponding heart counts (4 = no background correction; 5 = background correction using rectangular perirenal area; 6 = background correction using subrenal area); 7 = Patlak-Rutland algorithm, including double background correction. A = use of 3 early points of renogram (1 min, 1 min 20 s, 1 min 40 s); B = use of 4 early points of renogram (1 min, 1 min 20 s, 1 min 40 s, 2 min); C = use of 3 early points of renogram (1 min 20 s, 1 min 40 s, 2 min).

calibrated for surface area and (c) quadrangular subrenal area calibrated for surface area.

Patlak-Rutland Plot. The Patlak-Rutland plot combined a specific algorithm and a specific background correction and was applied to the renal curve after an initial correction using the perirenal area. The purpose of this method is to eliminate the part of the vascular background not corrected by the simple perirenal area subtraction (*11*). For each time interval, the renal counts (after subtraction of calibrated perirenal area) divided by the counts in the cardiac area (representing plasma activity) were plotted against the integral of the cardiac counts divided by the cardiac counts. A fit was obtained on the early part of the plot. The ordinate at origin represented the residual vascular activity, and the slope of the fit represented the relative uptake.

Choice of Time Interval. Three time intervals were chosen: (a) between 60 and 100 s, (b) between 60 and 120 s and (c) between 80 and 120 s. The first point of the renogram then was shifted to have the first appearance of the heart activity on the first image (a 20-s delay of arrival was sometimes observed). The same three combinations of points were then used after having shifted the first point.

In total, seven types of algorithms and background correction and six time intervals were used, giving rise to 42 combinations for each patient. For each combination, a relative left and right percentage uptake was calculated.

Analysis of Reproducibility. The difference between first and second measurements was calculated for each patient. As an example, if the right kidney uptakes were 48% and 45%, respectively, for the first and the second measurements, then the difference was noted as 3%. The mean of these differences represented the systematic bias between the two measurements; the SD of these differences represented the precision of the technique (Table 1).

Accuracy

Eighteen successive patients (13 children over 2 y and 5 adults) who underwent both ^{99m}Tc-DMSA and ^{99m}Tc-MAG3 examinations were included in this study. The clinical indication was the follow-up of urinary tract infection with or without associated vesicoureteral reflux. Patients with hydronephrosis, acute pyelonephritis or renal failure were excluded. All patients had normal or moderately impaired overall renal functions (^{51}Cr-ethylenediaminetetraacetic acid [EDTA] clearance, 70–197 mL/min/1.73 m^2) and a relative right ^{99m}Tc-DMSA percentage uptake between 21% and 70%. In 5 patients, the relative uptake was asymmetrical, outside the range of 30%–70%. In 6 patients, the ^{99m}Tc-DMSA and ^{99m}Tc-MAG3 studies were performed the same day. In these cases, ^{99m}Tc-DMSA was injected 2 h after ^{99m}Tc-MAG3, and the images were acquired 2 h later. At that time, the small residual ^{99m}Tc-MAG3 renal activity did not interfere with the high ^{99m}Tc-DMSA uptake. In the other 12 patients, the interval between both examinations was between 2 and 15 d.

^{99m}Tc-MAG3 Methodology. The same methodology was used as in the reproducibility study to yield 42 combinations of algorithms, background corrections and time intervals (Table 2).

^{99m}Tc-DMSA Scintigraphy. As in MAG3 study, scintigraphy was performed with the patient in the supine position, with the camera placed beneath the patient. Images were acquired 2–4 h after the injection of the tracer (adult dose 120 MBq, adapted for body size). One acquisition was obtained in the posterior view. Quadrangular ROIs were drawn manually over each kidney, and the relative percentage uptake was calculated using a small background correction from narrow regions just below and above each kidney. No correction was introduced for renal depth.

Analysis of Accuracy. With ^{99m}Tc-DMSA uptake as the reference method, we compared this percentage with the corresponding ^{99m}Tc-MAG3 relative uptake. For each patient, we calculated the difference between ^{99m}Tc-DMSA and ^{99m}Tc-MAG3 relative uptake for the kidney with the lowest uptake, taking into account the negative or positive sign of this difference. The mean of these differences represented the systematic bias between the two

TABLE 2
Accuracy of Relative Percentage Uptake in Patients with Both ^{99m}Tc-DMSA and ^{99m}Tc-MAG3 Examinations (SD of Differences in Kidney with Lowest Uptake)

Selection of points	Integral 1	2	3	Slope 4	5	6	Patlak-Rutland algorithm 7
A	2.8	1.9	2.1	4.6	3.3	4.5	2.5
B	2.7	1.8	2.0	5.0	4.0	4.6	2.4
C	2.5	1.8	1.9	6.2	5.3	5.5	2.7

Integral = summing up number of counts between two given points of renogram (1 = no background correction; 2 = background correction using rectangular perirenal area; 3 = background correction using subrenal area); Slope = first derivative of early part of renogram divided by corresponding heart counts (4 = no background correction; 5 = background correction using rectangular perirenal area; 6 = background correction using subrenal area); 7 = Patlak-Rutland algorithm, including double background correction. A = use of 3 early points of renogram (1 min, 1 min 20 s, 1 min 40 s); B = use of 4 early points of renogram (1 min, 1 min 20 s, 1 min 40 s, 2 min); C = use of 3 early points of renogram (1 min 20 s, 1 min 40 s, 2 min).

DMSA = dimercaptosuccinic acid; MAG3 = mercaptoacetyltriglycine.

measurements. A negative value means that the ^{99m}Tc-MAG3 relative uptake is systematically overestimated in comparison with the ^{99m}Tc-DMSA relative uptake, whereas a positive value means that the ^{99m}Tc-MAG3 uptake is underestimated. The SD of these differences represents the accuracy of the technique (Table 2). In 5 patients, the relative ^{99m}Tc-DMSA uptake was less than 30% for the kidney with the lowest uptake. A separate analysis of these data is presented in Table 3.

RESULTS

Reproducibility

No systematic bias was observed for the mean of the differences between the first and second measurements. For all methods, the mean of the differences was <0.3%.

The SD of these differences varied according to the method used (Table 1). The integral method gave the highest reproducibility. Only minimal differences (SD < 2%) were observed among the types of background chosen and even when no background at all was used (methods 1, 2 and 3). A change in the number of renal points did not affect significantly the reproducibility, even after shifting the first point.

The slope method resulted in a higher variability than the integral method (SD ≤ 10%), regardless of the type of background, the number and rank of renal points, the choice of time interval (methods 4, 5 and 6).

Double background correction using the Patlak-Rutland plot improved the results of the slope method, with 4 points used for the Patlak-Rutland fit. However, the variability was larger than with the integral method (SD = 2.8%), even after the shift of the first point (method 7B). The fit on 3 points (methods 7A and 7C) gave less satisfactory results (SD = 5.3%).

Accuracy

Entire Patient Group. Statistically, no systematic bias among the methods was observed for the mean of differences between ^{99m}Tc-MAG3 and ^{99m}Tc-DMSA relative uptake. The SD of these differences depended on the method used (Table 2). The integral and Patlak-Rutland methods gave comparable good results (no bias and SD < 3%). Only minimal differences were observed among the types of background chosen and even when no background at all was used (methods 1, 2 and 3). A change in the number of renal points did not affect significantly the accuracy, even after shifting the first point.

The slope method resulted in less accuracy than the integral method or the Patlak-Rutland plot (SD ≤ 6.3%), regardless of the type of background, the number and rank of renal points, the choice of time interval (methods 4, 5 and 6).

Patients with Asymmetrical Relative Uptake. In this group of 5 patients, higher systematic biases were observed for the integral method without background correction and for the slope method without background correction or with subrenal background correction. Among the remaining methods, the integral method, with perirenal or subrenal background correction, and the Patlak-Rutland plot combined the lowest mean and SD of the differences (Table 3).

DISCUSSION

Integral and slope methods are both commonly used for estimating the left-to-right ratio (*2–9*), and the type and amount of background to be subtracted are continually debated (*9,10*). The Patlak-Rutland plot has been advocated to improve the correction of the intrarenal intravascular background (*11–14*). However, we are not aware of previous studies investigating systematically the reproducibility and the accuracy of the left-to-right ratio.

The easiest way of testing reproducibility is to analyze retrospectively the results on patients who underwent the procedure twice without any clinical change between the two tests. The drawbacks of the method are obvious. Because the reason for performing both tests usually is related to a precise clinical question, one is tempted to exclude patients in whom great variations between the two tests were observed, reasoning that these variations were indeed the results of clinical events. We therefore chose to study prospectively the reproducibility of the ^{99m}Tc-MAG3

TABLE 3
Accuracy of Relative Percentage Uptake in Five Patients with Asymmetrical Relative Uptake (Mean ± SD of Differences in Kidney with Lowest Uptake)

Selection of points	Integral			Slope			Patlak-Rutland algorithm
	1	2	3	4	5	6	7
A	−4.2 ± 2.8	1.6 ± 2.5	−2.0 ± 1.4	3.5 ± 7.0	0.3 ± 4.4	2.7 ± 5.7	0.7 ± 2.8
B	−4.0 ± 2.5	1.5 ± 2.2	−1.8 ± 1.3	4.2 ± 7.2	1.1 ± 4.3	4.2 ± 5.5	0.7 ± 2.8
C	−3.7 ± 2.3	1.4 ± 2.1	−1.7 ± 1.2	4.4 ± 8.1	1.5 ± 5.0	5.1 ± 6.3	0.8 ± 3.2

Integral = summing up number of counts between two given points of renogram (1 = no background correction; 2 = background correction using rectangular perirenal area; 3 = background correction using subrenal area); Slope = first derivative of early part of renogram divided by corresponding heart counts (4 = no background correction; 5 = background correction using rectangular perirenal area; 6 = background correction using subrenal area); 7 = Patlak-Rutland algorithm, including double background correction. A = use of 3 early points of renogram (1 min, 1 min 20 s, 1 min 40 s); B = use of 4 early points of renogram (1 min, 1 min 20 s, 1 min 40 s, 2 min); C = use of 3 early points of renogram (1 min 20 s, 1 min 40 s, 2 min).

relative uptake on volunteers, each of whom was in a similar physiological condition at the time of both tests, accepting the drawback of testing the reproducibility only on volunteers with normal function.

The integral method, applied to ^{99m}Tc-MAG3 renography, appeared to provide the most reproducible results, regardless of the type of background chosen. Even no background correction gave excellent results.

The Patlak-Rutland plot gave better results than the slope method, obviously because of a better correction for background, but the results of both methods were not as good as those obtained with integral method. In a recent study on simulated ^{99m}Tc-MAG3 and ^{99m}Tc-DTPA renogram curves, Moonen and Jacobsson (*15*) found similar results. Their mean error induced by noise was highest for the slope method, lower for the Patlak-Rutland plot and lowest for the integral method.

Referring to Taylor et al. (*16*), we have tried to improve the results by standardizing the first point of the curve to the moment of appearance of the tracer into the heart. This correction, however, did not significantly modify the results of reproducibility, regardless of the algorithm chosen.

A method can be very reproducible but not accurate. For that reason, we tried to estimate the accuracy of the left-to-right ratio in patients who underwent both ^{99m}Tc-MAG3 renography and ^{99m}Tc-DMSA scintigraphy, successively and within a short time interval.

In patients with normal renal function or moderate renal impairment, the signal-to-noise ratio on ^{99m}Tc-DMSA scintigraphy was excellent. It seemed reasonable to take this ratio as the reference for estimating the accuracy of the left-to-right ^{99m}Tc-MAG3 uptake ratio, limiting the choice of patients to those with normal or moderately decreased overall clearance. We decided that this study could not be applied to patients with poor renal function, in whom ^{99m}Tc-DMSA uptake cannot reasonably be used as an acceptable gold standard.

The use of one single posterior view, noncorrected for kidney depth, may be questioned as a reference method. In fact, the relative percentage uptake may differ when using the geometric mean or when introducing SPECT methodology. However, this is unimportant in this study, because the aim was to evaluate the effect of renographic variables, such as time interval for renal counting, time of appearance of first cardiac activity and background correction, with both ^{99m}Tc-MAG3 and ^{99m}Tc-DMSA studies performed under the same conditions.

The integral method provided the greatest precision, regardless of the background area chosen. However, background subtraction appeared mandatory to avoid a systematic underestimation of the difference between left and right percentage uptake in patients with asymmetrical uptake. The results with the Patlak-Rutland plot were as good as with the integral method, but certainly not better, even in cases of asymmetrical uptake. Although the Patlak-Rutland plot might not be expected to provide better results, we have shown the robustness of this method previously by analyzing the characteristics of the Patlak-Rutland fit (*17*). This robustness does not imply that the accuracy of the method is necessarily superior to the traditional integral method, at least for relative measurements. The high statistics of counting inherent to the integral method might be more beneficial than the advantage of a better correction of the vascular component using the Patlak-Rutland fit. The slope method gave less accurate results. As in the reproducibility study, this is the result of low number of counts.

Finally, standardizing the first point of the curve to the moment of appearance of the tracer into the heart did not significantly modify the accuracy, using any of the algorithms.

CONCLUSION

In patients with normal or moderately impaired overall renal function, with either symmetrical or asymmetrical relative uptake, the methods that combine the best reproducibility and accuracy for estimating ^{99m}Tc-MAG3 left-to-right uptake ratio are the integral method, with subrenal or perirenal correction, and the Patlak-Rutland plot.

The use of the integral method without background correction introduced a systematic bias, whereas the slope method resulted in high variability. Therefore these methods cannot be recommended. It should be emphasized that this article is devoted to relative uptake and the conclusions cannot be applied to the measurement of absolute clearance.

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