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Reproducibility of Technetium-99m-MAG3 Clearance Using the Bubeck Method

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The objective of this study was to estimate the reproducibility of ^{99m}Tc-mercaptoacetyltriglycine (^{99m}Tc-MAG3) clearance calculated using a single-sample method. **Methods:** One hundred forty-seven patients with urological or ear, nose and throat cancer were analyzed in a retrospective study. Each patient had at least two clearance studies with ^{99m}Tc-MAG3 before chemotherapy treatments to monitor renal function. Up to five clearance studies per patient were considered. The reproducibility was estimated by comparing two consecutive investigations. Pairs of investigations with a change in split renal function of more than 5% or an interval of more than 50 days were excluded. Clearance was determined using the Bubeck method. For each pair of consecutive clearance data, the difference between the first and the second measurements was expressed as a percentage of the mean value of the two measurements. The mean of these normalized differences represents the systematic deviation, and the s.d. represents the reproducibility of the compared clearances. **Results:** After the selection, 242 pairs of consecutive clearance data remained for comparison. Significantly different clearances were observed only between investigations 0 and 1 and between 4 and 5. The systematic deviation of these comparisons totaled −3.8% and −5.7%, respectively. In the other comparisons, no significant deviation induced by the chemotherapy was found. The reproducibility calculated for all comparisons totaled 11.7%. **Conclusion:** The error of reproducibility of ^{99m}Tc-MAG3 clearance using the Bubeck method was ≤11.7%. This was an acceptable value, taking into account the greater fluctuation of tubular function compared with the glomerular filtration rate.

Key Words: clearance studies; technetium-99m-MAG3; Bubeck method

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Technetium-99m-mercaptoacetyltriglycine (^{99m}Tc-MAG3) has gained wide acceptance because of its high extraction rate compared with glomerular tracers. However, recent studies have shown that the reproducibility of ^{99m}Tc-MAG3 clearance with coefficients of variation of about 25% is low (*1,2*). This is alarming considering that those two studies were performed prospectively on healthy volunteers. The question arises whether the reproducibility of ^{99m}Tc-MAG3 clearance is poorer if patients are investigated under actual clinical conditions using a single-sample method for clearance determination. We therefore estimated the reproducibility of ^{99m}Tc-MAG3 clearance in patients both before and after chemotherapy.

MATERIALS AND METHODS

Patients

One hundred forty-seven patients with urological or ear, nose and throat (ENT) cancer (Table 1) were analyzed in a retrospective study. These patients had at least one to five cycles of a nephrotoxic chemotherapy. To monitor renal function (*3*), we performed clearance studies with ^{99m}Tc-MAG3 before each cycle of chemotherapy. Thus, a maximum of six clearance measurements per patient were included. The clearance studies were numbered from zero (baseline study) to five (last study before the fifth cycle of chemotherapy).

The chemotherapeutic drugs used are listed in Table 1. Reproducibility was estimated by comparing two consecutive investigations. Pairs of investigations indicating a change of split renal function of more than 5% or those performed over an interval of more than 50 days were excluded.

Clearance Measurements

All patients were hydrated orally with 10 ml/kg body weight 30 min before tracer administration. We injected 100–200 MBq ^{99m}Tc-MAG3 and performed a renal scan over the following 32 min in the supine position. For clearance determination, one or two plasma samples were taken by venipuncture opposite the injection site 20–40 min postinjection. Clearance was calculated using the Bubeck method (*4*). Regions of interest were drawn over and between the kidneys, representing the background. Time-activity curves were generated and the split-renal function was determined by the integrals of background-corrected time-activity curves between 60 and 100 sec. Studies showing ascending time-activity curves of the background (indicating an infiltration at the injection site) were excluded.

Statistical Analysis

The reproducibility was calculated according to the procedure published by Bland et al. (*5*): For each pair of consecutive clearance data, the difference between the first and the second measurement is expressed as the percentage of the mean value of the two measurements. The mean of these normalized differences represents the systematic error (bias) and the s.d. the reproducibility of the compared clearances. We expected that the normalized differences would be normally distributed (*5*). Therefore, 95% of these normalized differences fell within the 2-s.d. range. We also tested whether the compared clearance pairs were significantly different ($p \leq 0.05$, Wilcoxon pair test).

TABLE 1
Diagnosis and Chemotherapeutics of Patients Under Study

Tumor	n	Chemotherapeutics
Testicular cancer	87	Cisplatin, etoposide, bleomycin
Prostatic cancer	17	Cisplatin, epirubicin
Urothelial or bladder cancer	30	Methotrexate, vincristine, doxorubicin, cisplatin
ENT cancers	13	Cisplatin

ENT = ear, nose and throat.

TABLE 2
Mean and s.d. of Normalized Clearance Differences

Compared investigations	n	Mean (%)	s.d. (%)	Range	
0/1	100	0.3	11.7	91–415	ns
1/2	73	−3.8	13.5	138–397	*
2/3	29	0.3	10.0	165–330	ns
3/4	27	−4.4	10.0	171–334	ns
4/5	13	−5.7	9.2	154–321	*
All pairs	242	−0.36	11.7	91–415	

*$p < 0.05$.
n = number of compared clearance pairs; ns = nonsignificant.

RESULTS

Using the selection criteria (time interval ≤50 days and change of split renal function ≤5%), 242 pairs of consecutive clearance data remained for comparison. The mean of the normalized differences varied between 0.3% and −5.7% for the single comparisons (Table 2). If all comparisons are summarized, the mean amounts to −0.36%. Using the Wilcoxon pair test, only the clearance pairs ½ and ⅘ were significantly different. In these comparisons, the mean normalized deviation amounted to −3.8 and −5.7%, respectively. The s.d. of the normalized differences varied from 9.2 to 13.5 for single comparisons and amounted to 11.7% for all comparisons. The range of 2 s.d. of reproducibility extended from −24% to 24%.

DISCUSSION

Technetium-99m-MAG3 has gained increasing acceptance and is used for monitoring kidney function (*3*). For the correct interpretation of ^{99m}Tc-MAG3 clearance values, knowledge of reproducibility is important. Unfortunately, studies (*2,6,7*) do not show concordant results (Table 3). On the one hand, the listed ranges of 1 s.d. of reproducibilities varied between ±7% and ±25%; on the other hand, the maximum number of patients studied was 30. Therefore, the goal of the actual study was the examination of reproducibility of ^{99m}Tc-MAG3 clearance calculated according to a simple, widely used method in a larger number of patients. First, we had to critically examine the influence of chemotherapy and the retrospective data sampling in our study.

The influence of chemotherapy can be estimated using the mean values of normalized clearance differences (Table 2). They should be zero if there was no influence of chemotherapy on the kidney function. In our study, these mean values of

TABLE 3
Previous Studies on the Reproducibility of Technetium-99m-MAG3 Clearance

Author	n	Time interval	Reproducibility (%)
Piepsz et al. (*2*)	12	8 days	25
Kotzerke et al. (*1*)	30	< 1 Tag	6.3
Kotzerke et al. (*1*)	30	1 wk	40.4
Kotzerke et al. (*1*)	30	1 yr	11.7
Møller et al. (*7*)	17	5 days	12.4
This study	242	< 50 days	11.7

n = Number of compared clearance pairs; Time interval = time interval between compared investigations.

normalized clearance differences varied between 0.3% and −5.7% for the single comparisons. Only the clearance pairs ½ and ⅘ were significantly different ($p \leq 0.05$, Wilcoxon pair test). If all comparisons are summarized, the mean of normalized clearance differences amounted to −0.36%. These low values demonstrated that there were no considerable systematic deviations. Thus, the influence of a single cycle of chemotherapy was assumed to be small.

The second point that must be discussed is the retrospective data analysis because, unlike prospective studies, not all factors affecting kidney function and clearance determination can be controlled. These factors may increase the variance of clearance data. Thus, the reproducibility calculated in this study was worse than the value obtained under optimum conditions. The range of 1 s.d. of reproducibility calculated in this study was ±12% or less. This value was based on a large number of patients with 242 clearance pairs and was derived from routine clinical data. Because we used a common, simple, single-sample method (*4*), our value of reproducibility may serve as a guideline for other institutions working with the same method.

The range of 1 s.d. of reproducibility not greater than ±12% is consistent with the data from Kotzerke et al. (*1*), who also used the Bubeck method (*4*), calculating the reproducibility for three intervals (1 day, 1 wk and 1 yr), each in 30 patients. The ranges of 1 s.d. of reproducibility for 1 day and 1 yr amounted to 6.3% and 11.7%, respectively, and are consistent with our results as well as those of Møller et al. (*7*), who reported a reproducibility of 12.4% for 5 days. For a 1-wk interval, Kotzerke et al. (*1*) calculated a s.d. of normalized clearance differences of 40.4. However, after exclusion of three patients with a clearance lower than 100 ml/min per 1.73m^2, the s.d. was reduced to 16% (*1*). This suggests that reproducibility is worse in patients with poor kidney function. Unfortunately, our data did not contain enough clearances lower than 100 ml/min per 1.73 m^2 to prove this assumption.

The poorest reproducibility of ±25% was measured by Piepsz et al. (*2*). This is surprising because their investigation was performed prospectively and carefully on volunteers. The clearance was determined using multiple blood sampling according to the Sapirstein method, which is considered the reference standard. Simultaneously, Piepsz et al. (*2*) calculated the range of 1 s.d. of reproducibility of ^{51}Cr-ethylene diaminetetraacetic acid (^{51}Cr-EDTA) clearance to be ±8.4%. The systematic deviation of intraindividually compared clearance values was 2.1% and 20% for ^{51}Cr-EDTA and ^{99m}Tc-MAG3, respectively. According to Bland et al. (*5*) on which our data analysis and that of Piepsz et al. (*2*) was based, the calculation of reproducibility is not possible in the presence of large systematic deviations. For ^{99m}Tc-MAG3 clearance, these deviations totaled 20% in the data of Piepsz et al. (*2*), compared with −3.8% in our data. The reason for this discrepancy is speculative. Piepsz et al. (*2*) explained that the systematic deviation of the ^{99m}Tc-MAG3 clearance values may be caused by psychological stress because the patients were not as familiar with the investigation procedure the first time as they were the second time. They referred to the study of Grady et al. (*8*), who found a lower renal blood flow in rats under stress. This was, however, contradicted by the findings of Fauvel et al. (*9*). They measured glomerular filtration rate (GFR) and effective renal plasma flow (ERPF) using inulin and *p*-aminohippuric acid, respectively, in 15 volunteers at rest and under psychological stress. Whereas the filtration fraction increased significantly ($p \leq 0.05$) and sodium excretion tended to decrease, there were no changes in GFR or ERPF. A second possible reason for the discrepancy between our data and those of Piepsz et al. (*2*) may be the patients' different degrees of hydration. In contrast to Piepsz et al. (*2*), who used standard oral preparation of approximately 0.5 liter of fluid, our patients received more fluid with at least 10 ml/kg body weight. The importance of hydration for reproducibility has been emphasized by Frokiaer et al. (*10*), who measured the clearance of hippuran in pigs at varying urinary flow rates. The reproducibility was fair at the same urinary flow rates but was significantly poorer at different flow rates.

There is no doubt that the clearance of ^{51}Cr-EDTA is more reproducible than that of ^{99m}Tc-MAG3. Thus the range of 2 s.d. of reproducibility amounts to ±24% (actual study) for ^{99m}Tc-MAG3, in contrast to ±16.8% for ^{51}Cr-EDTA (*2*). Note however, that ERPF and tubular function are subject to larger physiological fluctuations than GFR. Therefore, the clearance of tubular secreted agents measured at different times must be less reproducible than glomerular filtrated agents. Therefore, a priori, it is obvious that radiopharmaceuticals measuring GFR have a better reproducibility than agents measuring the ERPF or the tubular extraction.

As Rehling et al. (*11*) demonstrated, this not only concerns ^{99m}Tc-MAG3 but also other tubular secreted agents. In simultaneous measurements with ^{99m}Tc-MAG3, ^{125}I-orthoiodohippurate (^{125}I-OIH) and ^{51}CR-EDTA, they found that the clearance ratio of ^{99m}Tc-MAG3 to ^{125}I-OIH had a lower coefficient of variation (13.4%) than the ratio of ^{99m}Tc-MAG3 to ^{51}Cr-EDTA (31.2%).

Also, in classic agents such as inulin and *p*-aminohippuric acid, a poorer reproducibility has been found in measuring ERPF than GFR in rats (*12*). Even if the reproducibility of the clearance of tubular secreted substances is poorer than that of glomerular filtrated agents, their advantages (e.g., high extraction rate and better imaging) should not be forgotten. Radiopharmaceutical selection should be adjusted specifically to fit the clinical situation.

We expected that the normalized differences calculated in this study would be normally distributed (*5*). Therefore, 95% of these differences fell within the range of 2 s.d.. This means that a difference of two clearance values in the same individual of more than ±24% corresponds to a real change in kidney function ($p \leq 0.05$). Differences of clearance values smaller than ±24% should be interpreted more carefully.

CONCLUSION

The clearance of ^{99m}Tc-MAG3 is less reproducible than the clearance of glomerular filtrated agents. However, a change of ^{99m}Tc-MAG3 clearance of more than 24% in consecutive measurements in the same individual corresponds to a real change in kidney function with a confidence interval of ±95% if:

1. The method of clearance determination (Bubeck method) (*4*), hydration with more than 10 ml/kg body weight, as employed in this study, is used.
2. The two clearance measurements are less than 50 days apart.
3. MAG3 clearance is higher than 100 ml/min per 1.73 m^2.

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Comparison of Radionuclide Scrotal Blood-Pool Index Versus Gonadal Venography in the Diagnosis of Varicocele

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The purpose of our study was to assess the value of a radionuclide scrotal blood-pool index (SBPI) in diagnosing and grading clinical and subclinical varicocele. **Methods:** Scrotal scans were performed on 1360 infertile patients. Thirty fertile patients with a normal scrotum on palpation served as controls. The patients' red blood cells were labeled in vivo by administration of stannous ions of pyrophosphate followed by the intravenous administration of ^{99m}Tc-pertechnetate. The scans initially were inspected visually and, when bilateral varicocele was excluded, a computerized analysis of the ratio of the blood-pool activity in each hemiscrotum (SBPI) permitted accurate grading of the varicocele. A subgroup of 224 patients was selected randomly and had gonadal venography. The results of physical examination, scrotal scan, gonadal venography and semen analysis were compared. **Results:** Normal values of SBPI (0.9–1.1) were derived from the control group. There was a 93.5% correlation between palpation and SBPI grade in diagnosing palpable varicocele. When compared to gonadal venography, subclinical varicocele was demonstrated by scrotal scan in 54.8% of infertile male patients with abnormal semen analysis, normal female partners and no other cause of infertility. Of these patients, 32.6% had, unexpectedly, Grade 2 or 3 varicocele. Right and bilateral varicocele were demonstrated three times as often by scrotal scan than by palpation. SBPI was accurate in diagnosing recurrent varicocele but there was a low correlation (61.1%) between SBPI and gonadal venography grade. There was a high correlation between SBPI grade and sperm analysis grade. **Conclusion:** SBPI grading of varicocele was validated as an accurate, quantitative and noninvasive method of grading varicocele, equivalent to the grading system by palpation in a large group of infertile patients. The main contribution of SBPI was in detecting and grading subclinical varicocele in infertile patients with no other cause of infertility. SBPI also was accurate in diagnosing but not in grading recurrent varicocele.

Key Words: scrotal blood-pool index; gonadal venography; semen analysis; clinical and subclinical varicocele

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Varicocele is defined as a pathologic distention of the veins of the pampiniform plexus. Reflux of blood from the internal spermatic vein (ISV) resulting from the absence or incompetence of the venous valves may be present (*1*).

Varicocele occurs in 8% to 20% of men in the general population (*2–4*) and in 17% of men with proven fertility (*5*). The incidence of varicocele in men attending infertility clinics ranges from 19% to 41% (*6*). In a multicenter study by the World Health Organization (*7*), varicocele was present in 11.7% of the total male population and in 25.4% of the men with abnormal semen parameters who were evaluated for infertility of at least 1 yr duration.

Subclinical varicocele is defined as reflux through the internal spermatic vein without any palpable distention of the pampiniform plexus (*8*). Clinical varicocele is graded as Grade 1, 2 or 3 by the classification of Dubin and Amelar (*9*). Some authors suggest that larger clinical varicoceles are more likely to damage spermatogenesis than smaller clinical varicoceles (*7,10,11*). Progressive deterioration in sperm concentration and motility also was reported (*7*).

The purpose of our study was to assess the value of radionuclide blood-pool imaging of the scrotum in diagnosing and grading infertile patients with clinical or subclinical varicocele. A quantitative evaluation of the results was performed and the results were expressed as the nuclear scrotal blood-pool index (SBPI). The results of scrotal scintigraphy were correlated with the findings on clinical examination, gonadal venography and semen analysis.

MATERIALS AND METHODS

Scrotal scans, performed on 1360 patients (age range 17–52 yr; mean age 30.6 yr) from 1988 to 1994, were evaluated prospectively. The subjects were referred to our nuclear medicine department from infertility clinics and had been infertile for at least 12 mo before the evaluation. All these patients had at least three abnormal semen analyses. Primary palpable varicocele was present in 458 patients and recurrent varicocele in 135 patients. In 767 patients with normal women partners, no apparent cause of infertility was found after an extensive work-up and subclinical varicocele was suspected. From the group of 1360 patients, 224