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Original

Reassessment of the reproducibility of Technetium-99m mercaptoacetyltriglycine renal clearance

Carlos De Sadeleer, Marianne Tondeur, Bernard Georges, Hamphrey R. Ham, Amy Piepsz

Department of Radioisotopes, C.H.U. Saint Pierre Brussels, Belgium

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Abstract

BACKGROUND: Conflicting results have been published concerning the reproducibility of Tc-99m MAG3 clearance.
The aim of the study was to reevaluate again this reproducibility on a large prospective series of healthy volunteers.
MATERIAL AND METHODS: Fifty subjects underwent three successive tests performed at 1-week interval. The physiological conditions were controlled as much as possible and all experimental measurements were rigorously double-checked. Renal clearances were calculated using single sample algorithms.
RESULTS: Thin layer chromatography demonstrated a radiochemical purity of more than 92% (mean 93.8%; SD 1.6%; range 92.0–96.4%). The mean (and SD) of 44th minute plasma concentrations for the three successive measurements were respectively 1.8 ± 0.4, 2.1 ± 0.4 and 1.9 ± 0.4 (%dose/liter). The mean changes (and S.D. of differences) between two tests were 0.26 ± ± 0.29, –0.08 ± 0.5 and 0.18 ± 0.30 respectively between tests 1 and 2, tests 1 and 3, and tests 2 and 3.
Using Bubeck's algorithm, the mean clearance values (ml/min/ /1.73 m^2) were 268.8 (range 201.4–336.8), 247.2 (range 170.5– –290.3), and 262.8 (range 187.4–340.0) respectively for the first, second and third measurements. Using Russell's approach, the mean clearance values were respectively 314.9 (range: 208.7–441.7), 280.1 (range: 167.5–358.6), and 305.4 (range: 189.5–447.9).
CONCLUSIONS: High differences were observed between the 3 tests. Using Russell´s formula, the SD of differences between two tests was respectively 35.8, 47.7 and 57.7 ml/min/1.73 m^2 between tests 1 and 2, tests 1 and 3, and tests 2 and 3. Whether such a large variability is acceptable in clinical practice depends solely on what the clinician is expecting.
Key words: Tc-99m MAG3, clearance, precision, reproducibility, Russell, Bubeck

Correspondence to: Carlos De Sadeleer
Borrekent 51, 9450 Haaltert, Belgium
Tel: (+32 54) 325 607, fax: (+32 54) 518 151
e-mail: cdesadeleer@skynet.be

Introduction

Because of its high extraction rate and its excellent imaging properties [1–6], Tc-99m MAG3 is considered by many as the tracer of choice for renography. On the other hand, the use of this tracer for evaluating renal clearance remains controversial. Indeed, to be useful, the measurement of clearance should be reproducible. In this respect, conflicting results have been published [7–12]. Some authors [8, 10–12] have found a good reproducibility while others [7, 9] reported rather bad results.

The purpose of the present study was to reevaluate this intra-individual reproducibility on a large prospective series of normal volunteers, who underwent three successive tests, performed at 1-week interval. The physiological conditions of the subject were controlled as much as possible and all experimental measurements were rigorously double-checked.

Material and methods

Volunteers

Fifty healthy volunteers (19 males, 31 females) were enrolled in this study. They had a mean age of 29 years and a median age of 25 years (range 18–56 years).

They had no previous history of renal disease and their blood pressure was normal. None of them was receiving any medication.

The local ethical committee approved this study and written informed consent was obtained from all subjects prior to the examinations.

The fifty volunteers underwent three successive tests, all performed in the morning at 1 week interval. They had a light breakfast prior to the investigation and were asked to have the same breakfast for the three consecutive tests. At arrival in the department, they were extra hydrated with 33 cc. of water half an hour prior to the tracer injection and another 33 cc. of water between the tracer injection and the blood sampling.

The volunteers remained sitting in the department until the end of the plasma sampling (44 min. after injection).

The whole procedure was then repeated one week and two weeks later under exactly the same physiological conditions.

Each volunteer was injected approximately at the same hour for the three successive tests.

Tracer, dose, standard

Tc-99m MAG3 was prepared just before administration, in accordance with the recommendations of the manufacturer, using freshly eluted Tc-99m-sodium pertechnetate from a commercial Mo-99/Tc-99m generator (Ultratechnekow FM, Tyco Mallinckrodt Medical, Petten, Holland). All the doses prepared for the three consecutive tests were issued from the same batches (Technescan MAG3, Tyco Mallinckrodt Medical, Holland). For each of the three tests, two Tc-99m MAG3 preparations were used in order to shorten the time interval between preparation and injection. For each preparation, two standards of the dose were prepared.

Immediately after each of the six labeling procedures, quality control of Tc-99m MAG3 was performed by thin-layer chromatography (TLC). The same investigator was in charge of all the labeling procedures, measurements and in vitro counting, under the supervision of the radiopharmaceutical company.

The dose and a standard of the dose were weighed with an accuracy of 0.1 mg.

The standard and the post-injection residue of the dose were measured at a constant distance from the gamma camera; the ratio of these two measurements was used to estimate the weight of the residue.

Injection of the tracer

Each volunteer received an intravenous injection of 18 MBq Tc-99m MAG3 — diluted up to 2 ml — using a Butterfly needle and a three-way system, and rapidly flushed twice with 10 ml saline. The injection was always performed by the same investigator.

After the injection, the arm was positioned in front of a gamma camera in order to detect any extra vascular escape of the tracer at the time of the intravenous injection.

The same amount of activity was injected for the three consecutive tests.

Radio waved synchronized clocks were used in order to minimize the error on indicating the time of injection and the time of blood sampling.

Blood sampling

One blood sample was drawn from the antecubital vein opposite to the injection site at 44 min. after tracer injection. The blood sampling was always performed by the same investigator.

Counting

A 1 ml aliquot of the standard and the serum sample were measured in duplicate in a well counter for 1 minute, with a statistical error of $< 1\%$.

Empty tubes were inserted among the samples for estimating background count rates and a correction was introduced for Tc-99m decay.

Clearance calculation

For the clearance determinations, two different algorithms were used: Bubeck´s formula, in which the plasma concentration is first corrected for body surface [6]; and Russell´s formula, in which the correction for body surface is introduced on the calculated clearance value [3].

Bubeck's formula:

$$\textit{Tc-99m MAG3 clearance} = a + b\ ln(ID/Cn_t)\ [ml/min/1.73m^2]$$

Where: $a = -517\ e^{-0.011.t}$; $b = 295\ e^{-0.016.t}$; ID = injected activity (cps); $Cn = C \times BS/1.73\ m^2$ = normalized plasma concentration (cps/l); C = plasma concentration (cps/l); BS (body surface) = = 10 ^ (LOG(W)*0.425 + LOG(L) *0.725–2.144); t = time of blood sampling post-injection [min]; W = weight [kg]; L = length [cm].

Russell's formula:

$$\textit{Tc-99m MAG3 clearance} = F_{max}\ (1 - (exp(-a(1/c - V_{lag}))))\ [ml/min]$$

Where: c — fraction of dose per liter of plasma [l^{-1}]; T — time between injection and withdrawing of sample, between 35–55 min [min]; $F_{max} = 0.0400\ t^2 - 8.20\ t + 915$; $a = 6.50 \cdot 10^{-6}\ t^2 - 8.60 \cdot 10^{-4}\ t + 3.91 \cdot 10^{-2}$; $V_{lag} = -0.00150\ t^2 + 0.0100\ t + 8.79$.

The result is then corrected for body surface.

Reproducibility

The reproducibility was assessed according to the procedure published by Bland and Altman [13].

The mean of the individual differences represented the systematic difference between the two measurements. The standard deviation of these differences represented the reproducibility (precision) of the technique.

A paired *t*-test was used to evaluate differences between the different measurements. Bonferoni correction was used to take into account the multiple comparisons.

Moreover, in order to evaluate the effect of the Tc-99m MAG3 preparations on the reproducibility, the volunteers were also stratified according to the moment of the test: group A patients (n = 19) were those who received for the three tests an early morning Tc-99m MAG3 preparation; group B patients (n = 15) were those who received for the three tests a late morning preparation; group C patients (n = 13) were those with irregular time schedule: early morning test on one day and late morning on another day.

Results

Radiochemical purity

TLC demonstrated a mean radiochemical purity of more than 92.0% on the six labeling procedures of MAG3 with Tc-99m (mean: 93.8%; S.D.: 1.6%; range: 92.0–96.4%). Free Tc-99m pertechnetate and impurities respectively amounted to 3.40 ± 0.99% and 2.76 ± 0.68%.

Exclusions

Among the 50 volunteers, three were excluded because they missed one appointment. No particular event (disease, emotional stress, and medication) occurred among the volunteers during the whole duration of the study.

In no case could significant local uptake at the place of injection be detected. Therefore, 47 sets of consecutive clearance data remained for comparison.

Reproducibility of TC-99m MAG3 clearance

Plasma concentration

The mean plasma values were respectively 1.8 ± 0.4, 2.1 ± ± 0.4 and 1.9 ± 0.4 (%dose/L) for the first, second and third test (Table 1). The plasma concentrations were higher ($p < 0.001$) for the second study than for the first or the third one, independently of the fact that the MAG3 preparation was an early morning one or a late morning one.

The mean changes (and SD of differences) between two tests were 0.26 ± 0.29, –0.08 ± 0.5 and 0.18 ± 0.30 respectively between tests 1 and 2, tests 1 and 3, and tests 2 and 3.

MAG3 clearance

The mean and SD of the clearance values are reproduced in Table 2, for the three successive measurements and the two different algorithms for clearance calculation.

Using Bubeck's method, the mean clearance value was respectively 268.8 ml/min/1.73 m^2 (range: 201.4–336.8), 247.2 ml/ /min/1.73 m^2 (range: 170.5–290.3), and 262.8 ml/min/1.73m^2 (range: 187.4–340.0) for the first, second and third measurements.

Using Russell's approach, the mean clearance value was respectively 314.9 ml/min/1.73 m^2 (range: 208.7–441.7), 280.1 ml/ /min/1.73 m^2 (range: 167.5–358.6), and 305.4 ml/min/1.73m^2 (range: 189.5–447.9) for the first, second and third measurements.

The MAG3 clearance was significantly lower on the second test ($p < 0.001$), compared to the first and third tests, for both Russell´s and Bubeck´s algorithms. No such differences were observed between the first and third tests.

The mean changes and the SD are reported in Table 2, and Figure 1 shows the Bland and Altman plot of individual differences.

Table 1. Mean plasma values according to the moment at which the volunteers were injected

				Mean plasma value			Difference		
	n			1	2	3	2–1	3–2	3–1
A	19	Mean	[%dose/L]	1.9	2.0	1.9	0.1	–0.1	–0.1
		SD	[%dose/L]	0.3	0.3	0.4	0.2	0.3	0.3
B	15	Mean	[%dose/L]	1.7	2.1	2.0	0.4	–0.2	0.3
		SD	[%dose/L]	0.4	0.5	0.4	0.2	0.4	0.3
C	13	Mean	[%dose/L]	1.8	2.2	1.9	0.3	–0.3	0.1
		SD	[%dose/L]	0.3	0.5	0.5	0.3	0.2	0.4
All	47	Mean	[%dose/L]	1.8	2.1	1.9	0.3	–0.1	0.2
		SD	[%dose/L]	0.4	0.4	0.4	0.3	0.5	0.3

Group (A) corresponds to those who received on the three days early morning Tc-99m MAG3 preparation; group (B) are those who received on the three days a late morning preparation; group (C) are those with irregular time schedule: early morning test on one day and late morning on another day; 1, 2, and 3 are the plasma values respectively for the first, second, and third measurements

Table 2. Mean clearance values according to Bubeck's and Russell's formulae

				Mean clearance value			Difference		
	n			1	2	3	2–1	3–2	3–1
Russell	47	Mean	[ml/min/1.73m^2]	314.9	280.1	305.4	–34.8	25.3	–9.5
		SD	[ml/min/1.73m^2]	52.9	43.2	53.4	35.9	47.7	57.7
Bubeck	47	Mean	[ml/min/1.73m^2]	268,8	247.2	262.8	–21.6	15.6	–6.0
		SD	[ml/min/1.73m^2]	30,7	26.7	30.5	21.9	23.4	30.3

1, 2, and 3 are the plasma values for respectively the first, second, and third measurement

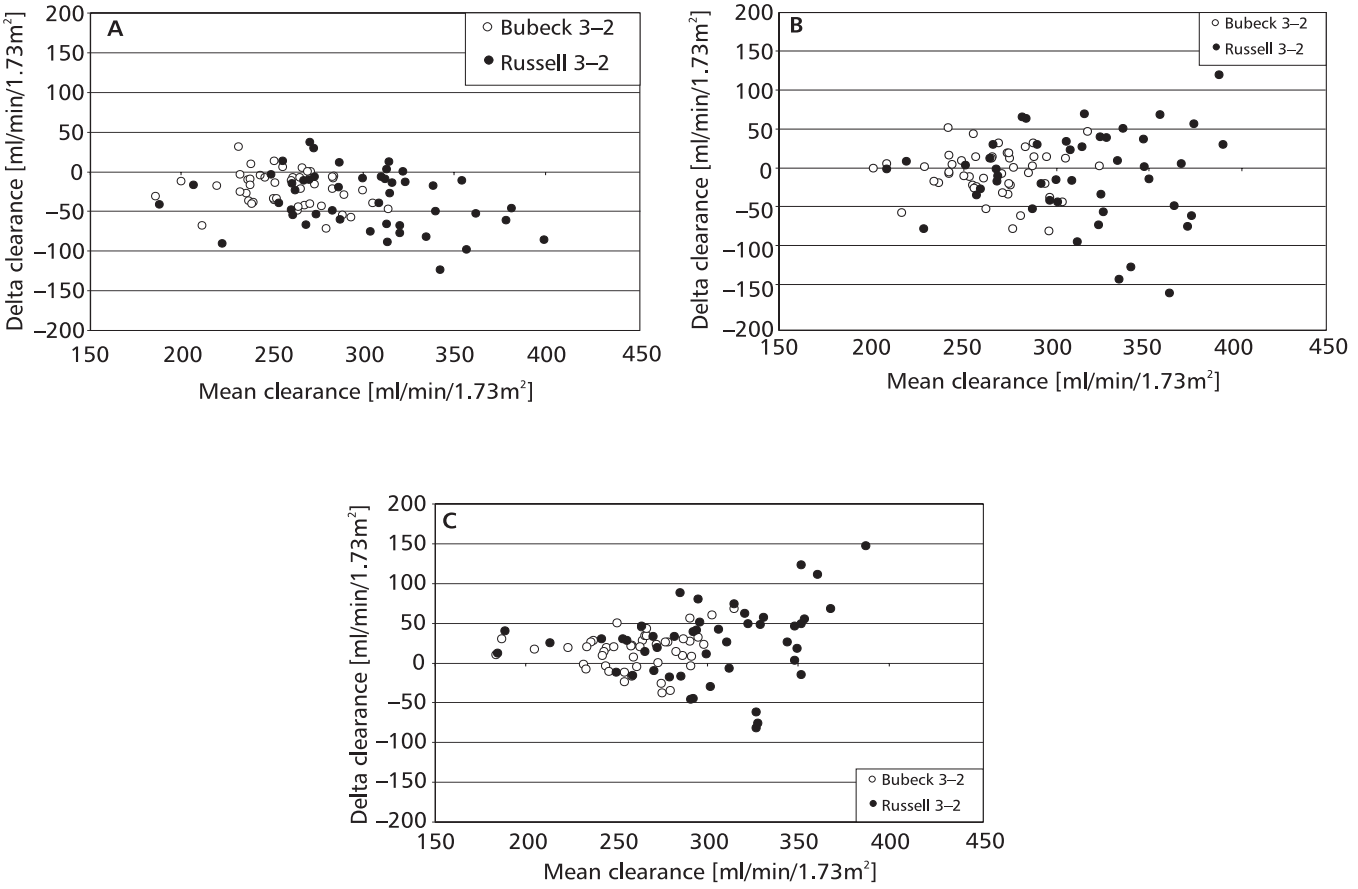

Figure 1. Bland and Altman plot. **A.** Comparison between the results of second and first tests. The abcis indicates the mean clearance value of the two tests. The ordinate shows the difference between the same two tests. The results obtained using Bubeck's algorithm are represented by open circles and those using Russell's algorithm by closed circles. The magnitude of differences for the individual subjects can be appreciated. The numerical values for the whole groups are presented in Table 2; **B.** Comparison between the results of third and first tests. The abscise indicates the mean clearance value of the two tests; **C.** Comparison between the results of third and second tests. The abscise indicates the mean clearance value of the two tests.

For all three tests, the coefficients of variation were smaller using Bubeck´s algorithm than using Russell´s algorithm.

Using Bubeck's algorithm, the mean changes were –21.6 ml/min/1.73 m² (SD: 21.9 ml/min/1.73 m²) between the second and first test, 15.6 ml/min/1.73 m² (SD: 23.4 ml/min/1.73 m²) between the third and second test, and –6.0 ml/min/1.73 m² (SD: 30.3 ml/min/1.73 m²) between the third and first test.

Comparison of the results obtained by Russell's approach showed a mean difference of –34.8 ml/min/1.73 m² (SD: 35.9 ml/min/1.73 m²) between the second and first test, a mean difference of 25.3 ml/min/1.73 m²(SD: 47.7 ml/min/1.73 m²) between the third and second test, and a mean difference of –9.5 ml/min/1.73 m² (SD: 57.7 ml/min/1.73 m²) between the third and first test.

Discussion

Tc-99m MAG3 is mainly excreted in the urine by tubular secretion. Because of its high extraction rate and the resultant higher signal-to-noise ratio, it is presently widely employed for gamma camera renography.

The determination of MAG3 plasma clearance by means of blood samples has also been advocated in children as well as in adults [1–6]. Most publications are either comparing Tc-99m MAG3 clearance with the excretion of other renal tracers [1, 2] or dealing with the determination of simplified clearance algorithms in children and adults [3–6].

However, since the purpose of clearance measurement is to appreciate any change of function related to disease or treatment, a good day-to-day reproducibility is required. This has recently been the focus of debate.

Theoretically, a proper evaluation of clearance reproducibility should be evaluated on subjects not suspected of having any disease which might result in improvement or deterioration of renal function.

Therefore, preference should be given to prospective investigations on human volunteers, not affected by any disease and investigated in well-controlled physiological conditions, rather than to bias-prone retrospective selection of patients. Moreover, the most accurate technique of clearance measurement should be applied. Using the biexponential fit on multiple blood samples taken from 12 healthy volunteers, Piepsz et al [7] found a poor reproducibility of MAG3 clearance compared to a good Cr-51 EDTA clearance reproducibility. Moreover, they observed a systematic bias, the clearance values observed during the first measurement being significantly lower than those observed during the second measurement.

Table 3. Previous studies on the reproducibility of Tc-99m MAG3 clearance

Authors	n	Prospective/ Retrospective	Volunteers/ Patients	Number BS	Method	Time interval	Mean (%)	SD (%)
Piepsz et al [7]	12	Prospective	Volunteers	15	Biexponential	1 week	–20.0	25.0
Kanazawa et al [8]	12	Prospective	Volunteers	2	Slope-intercept	1 month	–7.1	11.1
Kotzerke et al [9]	30	Prospective	Patients	1	Bubeck	< 1 day	–2.0	6.3
Kotzerke et al [9]	30	Prospective	Patients	1	Bubeck	1 week	–16.0	40.4
Kotzerke et al [9]	** 27	Prospective	Patients	1	Bubeck	1 week	6.0	15.7
Kotzerke et al [9]	30	Prospective	Patients	1	Bubeck	1 year	–1.5	11.7
Werner et al [10]	242	Retrospective	Patients	1	Bubeck	< 50 days	–0.36	11.7
Russell et al [11]	197	Retrospective	Patients	1	Russell	Repeated Measurements	Fit	12.0*
Möller et al [12]	17	?	Patients	?	?	5 days	?	12.4

* combination of 2 tracers — use of a conversion factor MAG3 to Hippuran; ** only patients with clearances > 100 ml/min were taken into account

Referring to previous animal experiments and human studies [14–16], the authors postulated that a stress factor, related to the heavy methodology they were using, might have induced the initial low clearance values they observed.

Further studies, using different approaches, appeared later on: retrospective studies on patients [10–12] or prospective investigations on volunteers [8]; single sample [9–11] or two-sample plasma clearance [8]; clearance calculation by means of slope intercept method [8], Bubeck's [9–10] or Russell's [11] algorithms. The variability observed was between 12 and 40 % with [7–9] or without [10] a systematic difference between the successive clearance determination. Depending on the authors, acceptable [8, 10––12] or unacceptable [7, 9] reproducibility was the final conclusion.

Because of these conflicting results, it was decided to start a new prospective experiment on a large number of healthy volunteers, in rather strictly determined physiological conditions (same hour of tracer injection, similar state of hydration, protein load and level of physical activity). In order to minimize as much as possible the stress factor related to an unknown procedure as postulated in previous studies [8–11], the simplified one blood sample technique was chosen. Moreover, it was decided to repeat three times the whole procedure, considering that the potential stress factor would preferentially affect the first measurement.

In this type of study, quality control at the various steps of the methodology is essential. The purity of the MAG3 preparations was systematically checked and was considered as acceptable according to the specifications of the manufacturer. Moreover, in order to detect any systematic difference related to an imperfect preparation, two preparations were used for each of the three experimental mornings.

Another factor that might significantly affect the result of the clearance is the measurement of the injected dose, standard, dilution of the standard and plasma samples. Therefore, the same experienced technologist performed these measurements and introduced elements allowing a quality control: samples measured in duplicate; measurement of dose and standard using a high precision balance.

Because of the large number of clearance measurements performed each day, a team of 9 people (medical and technical staff) participated to the study at different steps of the investigation (checking recent history of disease or stress, intravenous injection, checking of the possible paravenous injection, blood sampling). Radio waved synchronized clocks were also used, since errors in estimating the time interval between tracer injection and blood sampling may significantly affect the result of the clearance.

Finally, it was decided to apply the single sample algorithm proposed by Russell [3] for the calculation of MAG3 clearance. It has indeed been shown [17] that this technique provides results which are highly correlated with the multiple blood sample technique taken as the reference. On the contrary, the results obtained with Bubeck's algorithm are less good, particularly for the normal and high clearance range, where this algorithm clearly underestimates the true values. As the present study concerned normal volunteers, one could predict an artificial compression of the values at this clearance level using Bubeck's algorithm. However, since several studies on MAG3 reproducibility were based on this last formula, it was decided to calculate clearance using both algorithms, for the purpose of comparison.

The results show that the individual plasma concentrations were significantly higher at the second examination than at the first or the third examination. As a consequence of this, whatever the algorithm used, the clearance values were significantly lower during the second examination compared to the two others. The reason for this systematic difference is unclear. Stress, as postulated in previous studies [8–11], cannot explain the lower clearance observed during the second test. Similarly, methodological errors at the various steps of the procedure cannot be responsible for such a difference. Having in mind the possibility that such a difference would occur, it was decided that, for each experimental day, two different MAG3 preparations would be used. Since each volunteer was generally tested around the same hour on the three successive days, it was possible to classify the volunteers according to the preparation they received (group A, B and C). The analysis of these data clearly shows (Table 1) that the lower clearance values observed during the second series of experiments were not related to the MAG3 preparation, since the difference was observed for both preparations of the day. We can only introduce an additional hypothesis that the difference could be related to the Mo-99/Tc-99m generator. We cannot exclude that, despite having respected all the manufacturer's recommendations, some impurities due to the Mo-99/Tc-99m generator might have affected both final preparations of the second day.

For both the plasma concentrations and the clearance results obtained using Russell's algorithm, the variability was between 12 and 18 %, depending on the combination of tests 1, 2 and 3, and represents the true reproducibility of the MAG3 clearance. As expected, the variability observed with the Bubeck's method was less, but is due to an artificial compression of the clearance values [17].

Compared to the results previously observed using multiple blood samples [7], the level of reproducibility is better. Compared to the other studies on reproducibility, particularly those based on Bubeck's algorithm [9–10], the present results are at least as good (Table 3).

In this study a variability of 15% is observed. Two factors should be taken into account in interpreting the results. First, the present results were obtained using a single sample method. The error inherent to this method is included in the global results. Second, these results were obtained in an almost ideal experiment, which can not be reproduced in daily clinical practice.

The question arises whether a level of reproducibility around 15% is acceptable in clinical practice, knowing that two standard deviations may represent a variability of 115 ml/min. The answer is essentially depending on the expectations of the clinician.

If the aim is simply to obtain a gross estimate of the function (normal, impaired, strongly impaired), then a difference of 50 to 100 ml/min is probably unimportant.

The problem is essentially different if the effect of a disease, of a medication or a surgical treatment has to be estimated. In pelviureteric junction stenosis, for instance, the surgical decision is often based on a 10% decrease of the unilateral function [18]. It is clear that the level of reproducibility of MAG3 clearance found by us as well as by most of the other authors does not allow the use of Tc-99m MAG3 clearance for that purpose. Although repeated measurements in a given patient will reasonably describe, on a long course, the general trend of the renal function, the comparison of two successive tests is unable to estimate accurately the evolution of the renal uptake between these two successive tests.

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