

^{99m}Tc-MAG3: Review of pharmacokinetics, clinical application to renal diseases and quantification of renal function

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About 14 years have passed since Fritzberg et al. developed ^{99m}Tc-MAG3 in 1986. The biological properties of this radiopharmaceutical are somewhat different from radioiodine labeled hippurate: it exhibits higher protein binding, slower blood clearance, higher extraction efficiency by tubular cells and larger excretion into the bile than the latter. Nonetheless, it has been widely used as the agent of choice for renal scintigraphy, diuresis renography, captopril augmented renography, and renal transplant. Renal scintigraphy with ^{99m}Tc-MAG3 can provide excellent image quality even in the presence of severely decreased renal function. ^{99m}Tc-MAG3 is also used as an alternative to radio-hippurate for quantitative measurement of effective renal plasma flow. In this review, I focused on its pharmacokinetics, simplified quantitative methods and clinical application in renal diseases.

Key words: ^{99m}Tc-MAG3, pharmacokinetics, renovascular hypertension, plasma sample method

INTRODUCTION

RADIONUCLIDE RENAL STUDY is the only method that provides information both on renal structure and function. The qualitative and quantitative information obtained from the study generally depends on the biological properties of the radiopharmaceuticals and sophisticated mathematical algorithms and empirical correlation studies. ^{99m}Tc-MAG3 (mercaptoacetylglycylglycylglycine) (Fig. 1) was introduced by Fritzberg et al.¹ in 1986. The biological properties of ^{99m}Tc-MAG3 are somewhat different from those of radio-hippurate which has an excellent properties as effective renal plasma flow radio-agent.^{1–24} However, it is now widely used as an alternative to radio-hippurate for the evaluation of nephro-urological diseases such as renovascular hypertension^{25–40} and hydronephrosis,^{41–50} indirect cystography⁵¹ and renal transplant.^{52–60} In addition, a simplified method for the quantification of renal function, which has been reported by several investigators,^{61–78} is quite useful in routine

practice. However, the estimates attained by those simplified plasma-sample methods are not entirely in agreement.^{70,79,80}

In this review, I focused on the pharmacokinetics, clinical application to renal disorders and quantitative algorithms, which will be helpful in routine clinical practice using ^{99m}Tc-MAG3.

PHARMACOLOGICAL PROPERTIES

Issues concerning the pharmacokinetic properties of ^{99m}Tc-MAG3 are summarized in Table 1. Renal and plasma clearance, renal handling and urinary excretion ratios of ^{99m}Tc-MAG3 have been identified in animals in comparison with radioiodine labeled hippurate (OIH).^{1–7} The extraction efficiency for HPLC-purified ^{99m}Tc-MAG3 under constant infusion in rats was 85%, which is higher than 69% for OIH.¹ Probenecid and paraaminohippurate (PAH) inhibit renal clearance of ^{99m}Tc-MAG3 more than that of hippurate.^{1,3} PAH had no effect on iothalamate which is a glomerular filtration marker. These findings highly suggest that the largest fraction of ^{99m}Tc-MAG3 is excreted through the proximal tubular cells of the nephron. The recent study in pigs by Rehling et al.⁷ indicates that the total plasma clearance and renal clearance of ^{99m}Tc-MAG3 are about 75% that of OIH. The distribution

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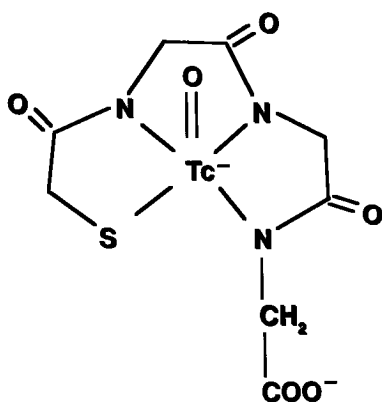


Fig. 1 Chemical structure of ^{99m}Tc -mercaptoacetyltriglycine (MAG3).

Table 1 Issues concerning the pharmacokinetic properties of ^{99m}Tc -MAG3

<i>Chemical</i>	
	Synthesis and radiolabeling
	Chemical structure
	Purification (HPLC-purified)
	Derivatives, D-, L-isomers
<i>Biological</i>	
	Clearance: renal, plasma
	Extraction efficiency
	Volume of distribution
	Protein binding
	RBC incorporation
	Inhibition by probenecid, paraaminohippurate
	<i>In vivo</i> distribution: hepatic uptake, biliary excretion
<i>Clinical</i>	
	Kit formation
	Clearance: correlation to OIH
	Volume of distribution
	Protein binding and effect of proteinuria
	Urinary excretion
	Renal transit (T_{\max} , $T_{1/2}$, MTT, C20/3)
	Relative renal uptake
	Image quality
	Administered dose for adults and children
	Application to diseases
	Radiation dosimetry

of volume of ^{99m}Tc -MAG3 is 71% that of iothalamate and 47% that of OIH. Protein binding is 90% for ^{99m}Tc -MAG3, 49% for OIH and 16% for iothalamate. RBC binding for ^{99m}Tc -MAG3 is (single injection/continuous injection) 1.0%/2.3%, which is significantly lower than 13.5%/9.0% for OIH and 3.1%/5.3% for iothalamate. The RBC binding is higher in the renal vein, which indicates incomplete back diffusion from RBC to plasma. It is more interesting and important that the renal plasma extraction of ^{99m}Tc -MAG3 is constant but significantly smaller after a single injection (0.54) than during continuous infusion (0.62). On the contrary, the renal plasma extraction of

OIH decreases continuously from 0.85 to 0.52 at 3–150 min postinjection. They concluded that the pharmacokinetic property of ^{99m}Tc -MAG3 of constant renal extraction is preferential to OIH as a tracer for renal function studies using a single injection technique.

In human studies, pharmacokinetic properties of ^{99m}Tc -MAG3 have also been identified in comparison with OIH or ^{99m}Tc -DTPA.^{8–24} Plasma clearance ratio of ^{99m}Tc -MAG3/ ^{131}I -OIH is estimated to be 1.07–0.44. The volume of distribution of ^{99m}Tc -MAG3 is less than that of OIH. The protein binding for ^{99m}Tc -MAG3 is 75–90% and 53–74% for OIH. The urinary excretion per injected dose in healthy persons is about 70% by 30 min postinjection, which is almost equal to or less than that for ^{131}I -OIH. It is agreed that ^{99m}Tc -MAG3 gives an underestimated plasma clearance in comparison to OIH, but plasma clearance of both radioagents correlates very well (Table 2). Plasma clearance of ^{99m}Tc -MAG3 that is estimated by established methods is lower than that of OIH. These differences in pharmacokinetic properties between ^{99m}Tc -MAG3 and OIH in human beings are due to higher protein binding, lower distribution volume, and different tubular extraction efficiency of ^{99m}Tc -MAG3. Under the consideration of these pharmacokinetic differences of ^{99m}Tc -MAG3 and OIH, Bubeck et al.¹¹ chose the expression “Tubular Extraction Rate (TER)” as a new parameter analogous to “ERPF” for OIH and “GFR.” They commented that TER might be used as a measure for the tubular function obtained with ^{99m}Tc -MAG3. Now, TER is used as a quantitative expression of function obtained by ^{99m}Tc -MAG3 renal study. However, most of clinicians is more familiar with ERPF as a renal function parameter than TER. When we convert TER to ERPF in routine practice, MAG3 clearance can be estimated from the equations in Table 1, or is simply divided by 0.53 to convert it to ERPF.⁷⁶

^{99m}Tc -MAG3 is now easily prepared using commercially available kit. Difference in pharmacokinetics between kit-prepared and HPLC-purified ^{99m}Tc -MAG3 have been discussed in the previous papers.^{81–86} So, when we compare pharmacokinetics of ^{99m}Tc -MAG3 with those of OIH and ^{99m}Tc -DTPA in animals and humans, we have to take the preparation of ^{99m}Tc -MAG3 into account. Kit-prepared ^{99m}Tc -MAG3 tends to have a higher biliary excretion than HPLC-purified ^{99m}Tc -MAG3.^{85,86}

CLINICAL APPLICATION TO RENAL DISEASES

As compared to ^{131}I -OIH, the biological properties of ^{99m}Tc -MAG3 seem to be inferior, but the physical properties for external imaging is superior. In addition, clinical availability of an instant kit is better than ^{131}I -OIH. Image quality with ^{99m}Tc -MAG3 is higher than that with ^{99m}Tc -DTPA in the presence of decreased renal function.^{10,13} Therefore, renal study with ^{99m}Tc -MAG3 is considered the first choice in routine practice.

Table 2 Linear regression and correlation of renal and/or plasma clearance between ^{99m}Tc -MAG3 and radio-hippurate

Reporters	Year	No. of patients	Clearance methods	Regression equation	Correlation coefficient
Bubeck et al.	1988	47	CI	$Y (\text{ml}/\text{min}/1.73 \text{ m}^2) = -2.90 + 0.66X$	0.95
Taylor et al.	1989	15	SI, SSM (60 min)	$Y (\text{ml}/\text{min}) = -12.6 + 0.55X$	0.87
Abdel-Dayem et al.	1989	19	SI, Schlegel	$X (\text{ml}/\text{min}) = -12.96 + 0.995Y$	0.95
Bubeck et al.	1990	124	CI	$Y (\text{ml}/\text{min}/1.73 \text{ m}^2) = 0.54 + 0.68X$	0.94
Muller-Suur et al.	1990	19	SI + 2CM (6s) for MAG3 SI, SSM (44 min) for OIH	$Y (\text{ml}/\text{min}/1.73 \text{ m}^2) = 26.134 + 0.4409X$	0.92
Bangni et al.	1990	103	SI, SSM (44 min)	$Y (\text{ml}/\text{min}) = 25.682 + 4.53X$	0.69
Kengen et al.	1991	14	CI	$X (\text{ml}/\text{min}/1.73 \text{ m}^2) = 4 + 1.87Y$	0.96
Itoh et al.	1993	16	SI, SS (44 min)	$X (\text{ml}/\text{min}) = 91.34 + 0.923Y$	0.95
	1993	20	SI, SSM (44 min)	$X (\text{ml}/\text{min}) = 84.92 + 1.078Y$	0.96

Y = MAG3 clearance, X = OIH clearance

Abbreviations: CI: continuous infusion, SI: single injection, SSM: single sample method, 2CM: 2-compartment model, Schlegel: Schlegel's uptake method

Renovascular hypertension (RVH)

Renal scintigraphy with an angiotensin converting enzyme inhibitor such as captopril is well known as captopril renography (CR) for the detection of renovascular hypertension. A renin-dependent kidney with unilateral, hemodynamically relevant renal artery stenosis (RAS) releases renin from the juxtaglomerular apparatus.^{25,26} Released renin promotes increased conversion of angiotensin I (AGI) to angiotensin II (AGII) in the lung. AGII in the circulation has a very strong pharmacological effect of peripheral artery contraction. As a result, systemic blood pressure is increased. These pathophysiological bases associated with renal ischemia are understood as renin-dependent RVH, Goldblatt's hypertension. AGII also contracts the efferent arteriole of the glomerulus rather than the afferent one. As a result, glomerular filtration is maintained as normal as possible. These pathophysiological phenomena are called "self-regulation" of the kidney. Glomerular filtration abruptly decreases after the administration of captopril which blocks conversion of AGI to AGII.

Diagnostic criteria for ^{99m}Tc -MAG3 in RVH are not essentially different from those for ^{99m}Tc -DTPA.²⁷ Captopril administration to a patient with RVH induces decreased renal clearance and prolonged renal transit.^{27,28,32-36} In consideration of the pathophysiological basis, CR with ^{99m}Tc -DTPA as glomerular filtration marker is theoretically preferable for detection of renal change to captopril in a renin-dependent kidney rather than ^{99m}Tc -MAG3 as the renal tubular radioagent. However, diagnostic accuracy with renal plasma flow markers such as OIH and ^{99m}Tc -MAG3 in RVH is not different from that with a glomerular filtration marker such as ^{99m}Tc -DTPA. Blaufox et al.³⁴ evaluated diagnostic accuracy of CR in RVH with simultaneous ^{131}I -OIH and ^{99m}Tc -DTPA administrations. There were no statistically significant differences in quantitative and qualitative accuracy, between OIH and DTPA or among quantitative parameters. The

highest accuracy for quantitative CR was 56% with DTPA (n = 57) and 60% with OIH (n = 60), in both cases using the relative renal uptake parameter. Accuracy may be improved by supplement use of *in vitro* simulated plasma renin activity. In individuals with renal insufficiency (n = 17, GFR < 50 ml/min), small kidney (n = 17) and/or bilateral renal artery disease (n = 16), about 50% of CR are abnormal but nondiagnostic. In patients with GFR of 10 ml/min/1.73 m² and/or split renal function of 10% or less, all quantitative and semiquantitative scintigraphic parameters were non-specific.³⁰ False-positive results were found in less than 5%.³⁴ As false positive causes, systemic hypotension during CR³⁷ and calcium antagonists³⁸ have been reported.

The investigation of CR in RVH has focused on changes of renal function in the affected kidney, namely individual kidney function. It is identified by Muller-Suur et al.³⁹ that global renal function assessed by ^{99m}Tc -MAG3 plasma clearance decreased in hypertensive patients with RAS but increased in patients without RAS. ^{99m}Tc -MAG3 clearance measurements during baseline and CR may not be informative for the detection of the affected kidney but can serve as additional diagnostic information on the presence of RVH in patients with hypertension.

A new approach, aspirin renography, has been described by Imanishi et al.³⁵ as possible to improve the diagnostic accuracy of captopril renography. The pathophysiological basis is that, in a patient with RAS, the synthesis of prostaglandin E₂ (PGE₂) is increased. The PGE₂ itself formed in glomeruli, and leads to an increase in renal blood flow but no increase in the GFR. However, PGE₂ as a vasodilator secondarily increases renin secretion and AGII production. As a result, it can have vasoconstrictive effects on the kidney. Administration of aspirin to a patient with RVH leads to inhibition of PGE₂ synthesis and reduces stimulation of the renin angiotensin system. In pathophysiological cascade of renal ischemia associated with RAS, aspirin plays a notable role similar

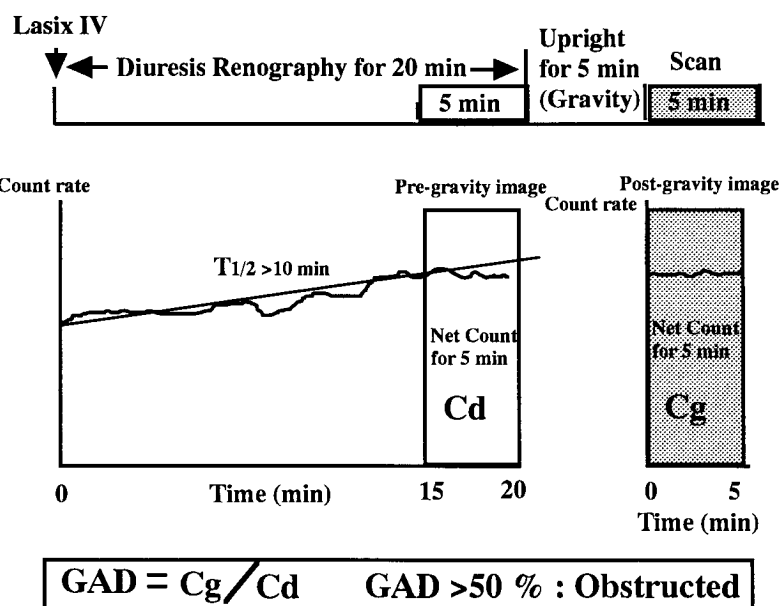


Fig. 2 The gravity-assisted diuresis renography illustrated from the paper by Wong et al.⁵⁰

to captopril. The method is theoretically very attractive. They concluded that aspirin renography was more accurate for the detection of RVH than CR. In a comparative study⁴⁰ between aspirin renography and captopril renography in 75 patients with hypertension, the sensitivities for unilateral RAS or bilateral RAS (i.e., stenosis that was at least unilateral) were, respectively 88% and 88% for captopril renography and 82% and 94% for aspirin renography (ns). The overall specificity was 75% for captopril and 83% for aspirin renography (ns). It was concluded that for the identification of RAS, the usefulness of aspirin renography equals, but does not surpass, that of captopril renography. Combined administrations of aspirin and captopril may be expected to be more effective than single administration of each drug.³¹ However, the combination study with aspirin and captopril may need further investigation in the future before it is accepted as a clinical application in RVH.

Diagnostic limitations of CR for identification of RVH have been disclosed even though the method is theoretically superior. It should be kept in mind that CR is utilized to identify the presence of AG II-dependent renal dysfunction but is also a good indicator to predict blood pressure response to revascularization. The positive predictive value of positive CR is 100%, while the negative predictive value of negative CR is 85%.³³

Hydronephrosis and Cystography

Diuresis renography (DR) is utilized to differentiate true obstruction (obstructed hydronephrosis) from a dilated non-obstructed system (stasis) by imaging after intravenous administration of furosemide. Diagnostic criteria^{43,47} used for DR have been established from clinical

data mainly based on ^{99m}Tc-DTPA. Urinary excretion of ^{99m}Tc-MAG3 is higher than ^{99m}Tc-DTPA. Therefore, ^{99m}Tc-MAG3 is considered to be preferable for the evaluation of urinary drainage to ^{99m}Tc-DTPA. Furosemide response was similar in both radioagents.^{10,45,50} Diagnostic accuracy depends on the load of diuretic before and during the study, preserved renal function and time of furosemide injection.^{41,48} In general, DR is considered to be higher in sensitivity than specificity, namely fewer false negative results and more false positive results. As a new modification, gravity-assisted drainage (GAD) was introduced by Wong et al.⁵⁰ This method can be helpful to differentiate between obstruction and non-obstruction in renal units with diuretic T_{1/2} > 10 min in a standard DR. The method and diagnostic criteria are illustrated in Figure 2. Using GAD > 50% in 62 renal units with T_{1/2} > 20 min in the standard DR, the sensitivity was 89.4%, the specificity was 83.9%, and the accuracy was 73.7%. Using GAD > 50% in 52 renal units with T_{1/2} = 10–20 min, the sensitivity was 100%, the specificity was 79.5%, and the accuracy was 82.7%. There was only one case of obstruction in 131 renal units with T_{1/2} < 10 min.

Indirect radionuclide cystography (IRC) with ^{99m}Tc-MAG3 is advocated as a favorable method rather than direct or indirect cystography with ^{99m}Tc-DTPA in children, because of its high extraction rate and non-invasiveness.⁵¹ However, ^{99m}Tc-MAG3 IRC missed two-thirds of refluxing kidneys. Using ^{99m}Tc-DMSA scintigraphy as reference, micturition cystoureterography detected 91% of the patients with DMSA abnormalities of at least one kidney, direct radionuclide cystography detected 95%, and IRC detected 46% and 43%, respectively, in groups of reflux grades I and II. Therefore, ^{99m}Tc-MAG3 IRC reflux

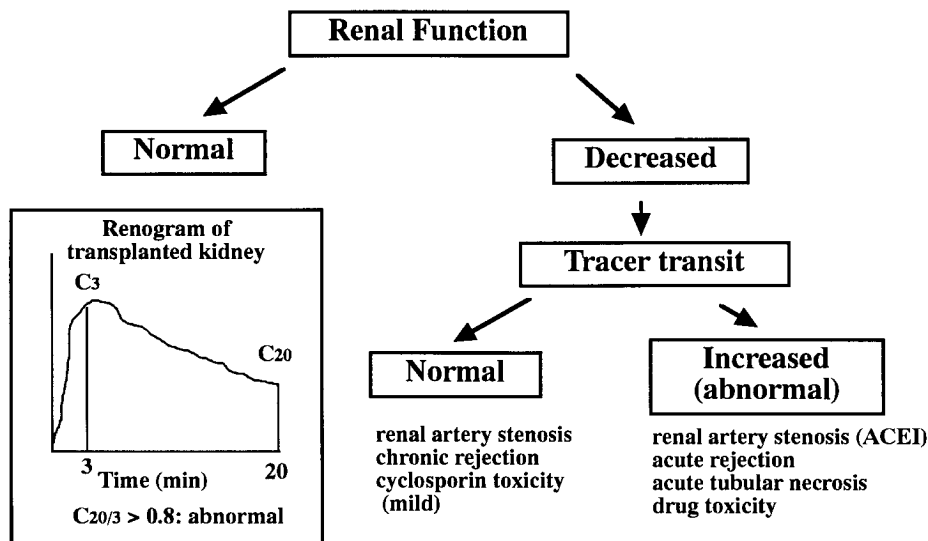


Fig. 3 Simple flow chart on differentiation of complications in transplanted kidney (from the paper by Dubovsky et al.)⁶⁰ and simple measurement of parenchymal transit index of C20/3 (from the paper by Li et al.).⁵⁵

cannot be utilized as the sole technique for the detection of vesicoureteric reflux.

Renal transplant

The assessment of function of a transplanted kidney is one of the major issues in radionuclide renal study. The medical complications after renal transplantation include surgical problems after anastomoses of vessels and ureter, rejection (superacute, accelerated, acute and chronic), cyclosporin toxicity to the kidney and acute tubular necrosis (ATN) which is commonly seen in the immediate post-transplantation period in cadaveric kidneys.⁵² ^{99m}Tc-MAG3, ^{99m}Tc-DTPA and ¹³¹I-OIH are all acceptable. Because of higher extraction efficiency, ^{99m}Tc-MAG3 is preferred over ^{99m}Tc-DTPA,⁵³ especially in patients with decreased renal function.^{54,60} There have been many indices of renal perfusion, renal function and transit time, which are utilized in the evaluation of medical complications.⁶⁰ Although medical complications such as acute rejection, ATN, chronic rejection and cyclosporin nephrotoxicity cannot entirely be differentiated from each other, a simple flow chart on differential diagnosis of medical complications after renal transplantation is summarized by Dubovsky et al.⁶⁰ Quantitated renal function and transit time are considered as important indices for differentiation of complications in the transplanted kidney. As a method of tracer transit index, Li et al.⁵⁵ proposed C20/3 in the renogram, which should be recommended for the differentiation of acute rejection from ATN, because of its technical simplicity and high diagnostic accuracy.

Renal failure

In acute renal failure, the radionuclide study is not only important for the diagnosis and the evaluation of pre-

Table 3 Methods on quantification of renal function using ^{99m}Tc-MAG3

<i>Plasma sample methods with or without urine sample</i>	
Steady-state infusion	
Single injection	
2 compartment model (plasma samples at least > 5)	
1 compartment model (usually 2 samples)	
Empirical single-sample method	
<i>External counting methods</i>	
Count-based uptake method	
Deconvolution analysis	
Patlak-Rutland's method	
2 compartment analysis with blood sample	
Whole body counting	

served renal function, but is also needed to access the potential of functional recovery or prognosis of the failed kidneys. In addition, it is often asked on the basis of the radionuclide renal study, whether the unilateral kidney with severely damaged function should be kept or removed in the operation. ^{99m}Tc-MAG3 is also useful in the evaluation of viability and prognosis in acute renal failure in renal transplantation.⁵⁷ Cortical uptake phase (CUP) image, which is a 2-min image acquired 1 min after ^{99m}Tc-MAG3 administration, is visually analyzed according to standardized semiquantitative guidelines. Interpretation is expressed in tubular injury severity score (TISS) that ranges from 1 (a normally functioning renal transplant) to 6 (a photogenic defect in place of renal transplant). All five patients with TISS of 5 and 6 lost the transplant. Only 1 of 10 patients with TISS of 4 lost the transplant. All patients (n = 49) with TISS of less than 4 recovered renal transplant function. They suggest that CUP image of ^{99m}Tc-MAG3 is an accurate prognosticator in patients

Table 4 Equations proposed for simplified single-plasma sample methods with ^{99m}Tc -MAG3

Reporter	Year	Population	Reference method	Equation
Russell et al.	1989	35 adults	2-compartment method with 8 samples	MAG3 Clearance (ml/min) $= F_{\max}(1 - \exp(-a(1/c - V_{\text{lag}})))$ c = fraction of dose per liter of plasma t = sampling time (35–55 min) $F_{\max} = 0.0400t^2 - 8.20t + 915$ $a = 6.50 \times 10^{-6}t^2 - 8.60 \times 10^{-4}t + 3.91 \times 10^{-2}$ $V_{\text{lag}} = -0.00150t^2 + 0.0100t + 8.76$
Bubeck et al.	1992	46 children 47 adults	gamma-camera with 2 plasma samples steady-state infusion	TER (ml/min/1.73 m²) = A + B ln(ID/cn_t) $A = -517e^{-0.011t}$ $B = 298e^{-0.016t}$ ID = injected dose (cps) t = time of blood sampling postinjection (min) $cn_t = C \times BS/1.73$ (cps/L/1.73 m ²) C = time-specific plasma concentration (cps/L)
Piepsz et al.	1993	98 children	2-compartment model with 5 samples (non-linear curve fitting)	Y (ml/min) = 657.07/(P(t)e^{-a(t-35)}) + 5.11 P(t) = %ID (L) of plasma at sampling time, t $a = 0.0298512$ t = 30–40 min
Russell et al.	1996	122 adults 80 children	2-compartment method (non-linear weighted regression)	MAG3 Clearance (ml/min) $= (222.6 - 168.8X + 52.72X^2 - 11.14X^3) \times W/t$ $X = \ln(p_t W)$ p _t = fraction of dose per liter of plasma at sampling time = t W = body weight (kg) t = sampling time: 45 min for adults 35 min for children

with early postoperative renal transplantation dysfunction. It is easy to understand that blood supply plays a critical role in the functional maintenance and recovery of the organ, of course the failed kidney. No and poor blood supply, namely no and poor early uptake of ^{99m}Tc -MAG3, indicates very low potential of functional recovery of the kidney. In this context, the early parenchymal uptake of ^{99m}Tc -MAG3 in the kidney may serve as an indicator of functional severity as well as functional recovery. The method must be applicable to acute renal failure due to any cause and also surgical manipulation of the kidney with very poor function (Fig. 3). In addition, the semi-quantitative parameters such as TISS should be altered to quantitative parameters such as kidney to background ratio, early renal uptake or TER. Clinical implementation of the methodology should be investigated in the future.

Quantitation of renal function

One of the major goals in radionuclide renal study is an appropriate evaluation of renal function in many diseases which may induce renal dysfunction. In that context, quantitative determination of renal function using renal radioagents is essential and important in radionuclide renal study. Radionuclide study using glomerular filtration markers is proved to be simple and most accurate in routine practice.⁷²

There have been several methods to quantify renal

function following a single injection (Table 3). The steady-state infusion method is most accurate for the determination of renal clearance. However, this method is technically complicated and is only performed in research study. The 2-compartment method after single injection is also proved to be accurate and is technically easier than the steady-state infusion method. Most clinical studies on the determination of plasma clearance employ this method. The 1-compartment method is practically easier than the 2-compartment method. In the determination of GFR with ^{99m}Tc -DTPA, the 1-compartment method with 2 samples is more accurate than the simplified single-sample method and is indicated to a patient with severely decreased GFR less than 20–30 ml/min in clinical practice.⁷² However, there is only one investigation that shows the relationship between 2-compartment and 1-compartment methods for the determination of ^{99m}Tc -MAG3 plasma clearance.⁶¹ Therefore, the 1-compartment method is considered not to play an important role in quantitative study using ^{99m}Tc -MAG3 in routine practice.

The external counting methods by gamma camera^{67,71,73–75,77,78} are very simple and give a simultaneous evaluation of renal function. These methods are useful in the evaluation of an individual kidney function and the determination of global kidney function in infants and children in whom blood drawing is often difficult. However, it is important to remember that not all children may

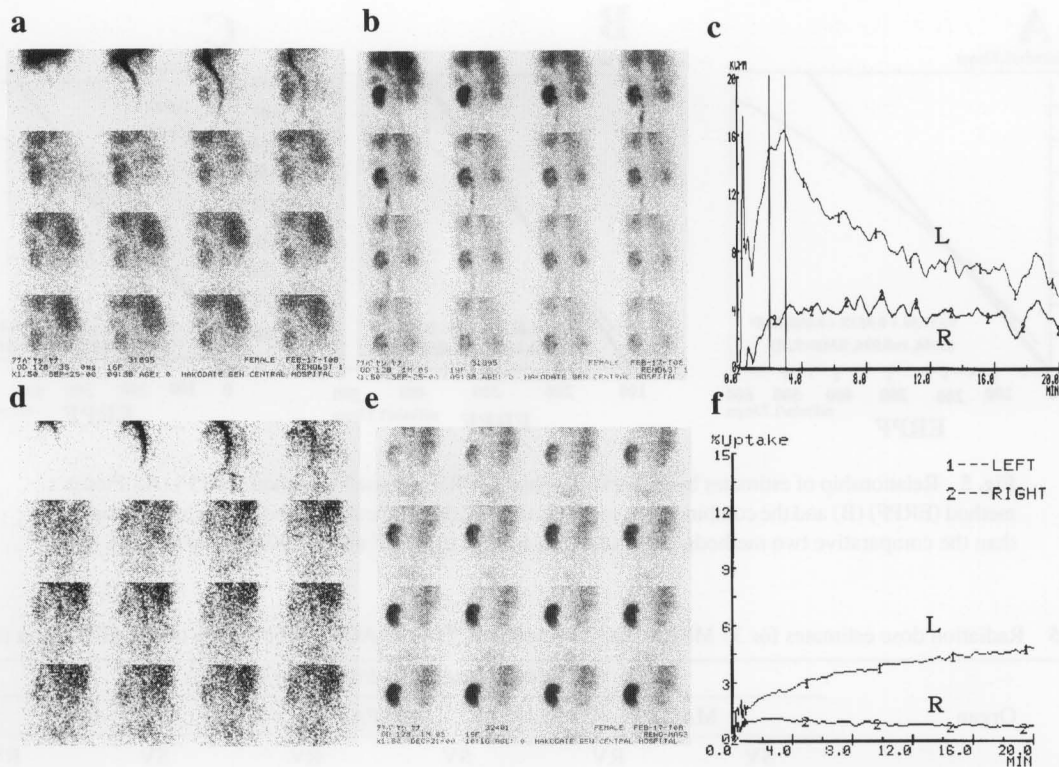


Fig. 4 Renal scintigraphy with ^{99m}Tc-DTPA (a–c) at the onset of acute renal failure and ^{99m}Tc-MAG3 (d–f) during hemodialysis about 3 months after the onset. The images with ^{99m}Tc-DTPA (a–c) show poor renal blood perfusion and uptake in the right kidney and decreased preservation of the GFR in the left kidney. ^{99m}Tc-MAG3 study also shows decreased renal perfusion of both kidneys and severely decreased preservation of TER in both kidneys, severer in the right than the left. ^{99m}Tc-DTPA study indicates that blood perfusion to the kidney is important as a prognostic indicator of functional recovery. ^{99m}Tc-MAG3 images identify that the right kidney has had no functional recovery and that the left kidney has poor potential of functional recovery. The early parenchymal image with ^{99m}Tc-MAG3 appears to be more useful in the evaluation of residual renal blood flow than the perfusion image.

have received an adequate percentage dose to constitute a reliably diagnostic study during the interpretation of the findings in pediatric radioisotope studies.⁶⁵ In addition, the gamma camera methods are considered to be inaccurate in the determination of global kidney function.^{72,78} All equations used in the gamma-camera uptake method are determined with a correlative study of plasma sample methods as reference. As long as the count-based gamma-camera method is based as reference for the plasma sample method for the determination of global renal function, it cannot overcome the accuracy of reference method.

Now, simplified single-sample methods are recommended for the determination of TER with ^{99m}Tc-MAG3.⁷² There have been 3 representative algorithms as single-sample method with ^{99m}Tc-MAG3 (Table 4). Bubeck's method^{62,64} is utilized for adults and children. Russell's method^{60,69} is also applicable to both. Piepsz's method⁶³ is dedicated to children. In comparison to Bubeck's and Russell's methods, Bubeck's method gives a significantly lower TER than Russell's method,^{70,79,80} particularly in

range of TER higher than 200 ml/min/1.73 m² (Fig. 4). I used to report that Bubeck's algorithm may be better than Russell's, because the former employed the steady-state infusion as reference.⁷⁹ On the contrary, the latter employed the 2-compartment method after single-injection as reference. Recently, it is reported that Russell's method may be better than Bubeck's.⁸⁰ It will become clear through further investigation which of the methods is preferable in routine practice. It will be also clarified whether accuracy and reliability of simplified single-sample method with ^{99m}Tc-MAG3 may depend on a level of preserved renal function, TER. Nonetheless, all simplified single-sample methods proposed until now are still recommended as the first choice for the determination of TER in both kidneys.

ADMINISTERED DOSE AND RADIATION DOSE

For adults, a relatively large range of activity is administered: 70–185 MBq for ^{99m}Tc-MAG3, 70–200 MBq for ^{99m}Tc-DTPA.⁷⁸ For dose adaptation in children, body

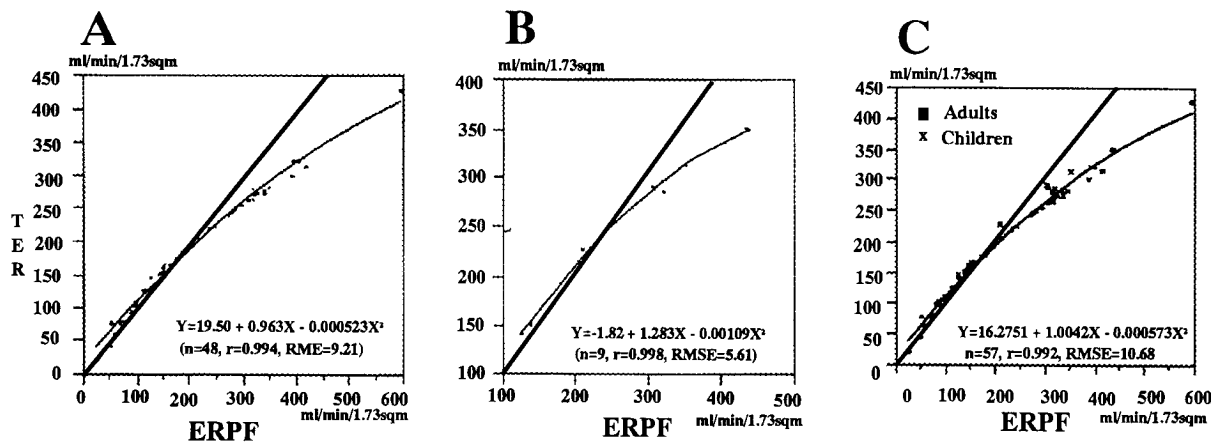


Fig. 5 Relationship of estimates by Bubeck's method (TER) to Russell's method (ERPF) (A), Piepsz's method (ERPF) (B) and the combined two methods (ERPF) (C). Bubeck's method gives lower estimates than the comparative two methods, particularly in a range of ERPF above 200 ml/min/1.73 m².

Table 5 Radiation dose estimates for 37 MBq (1 mCi) injection of ^{99m}Tc-MAG3, ^{99m}Tc-DTPA or ¹³¹I-OIH (from ref. 86)

Organ	Estimated radiation dose (mSv/37 MBq)					
	MAG3		DTPA		OIH	
	SV	RV	SV	RV	SV	RV
Kidneys	0.148	0.1443	0.1406	0.1369	0.555	0.518
Ovaries	0.2146	0.0851	0.1998	0.1258	0.777	0.2294
Red marrow	0.037	0.01813	0.0555	0.0444	0.1517	0.0592
Bone surface	0.0518	0.02479	0.0814	0.0666	0.1147	0.0444
Testes	0.148	0.592	0.1406	0.0888	0.592	0.1702
Urinary bladder wall	4.44	1.665	3.478	1.924	48.1	13.32
Uterus	0.481	0.1887	0.407	0.2442	1.776	0.518
Total Body	0.0518	0.02368	0.0666	0.0481	0.2331	0.0777
Effective dose equivalent	0.37	0.1554	0.3293	0.1998	3.293	0.089

SV: bladder voiding interval 4.8 hour, RV: bladder voided at 30 min, then at 4 hr and every 4 hr thereafter.

surface correction should be used and the minimum in children is recommended to be 15 MBq for ^{99m}Tc-MAG3 and 20 MBq for ^{99m}Tc-DTPA. The radiation dose of ^{99m}Tc-MAG3 is summarized in Table 5.⁸⁷ Rapid bladder voiding is essential to decrease the radiation dose to the patient. An effective dose with 37 MBq (1 mCi) of ^{99m}Tc-MAG3 and ^{99m}Tc-DTPA gives less radiation than a plain abdominal radiograph in adults (1.4 mSv, 0.05 mSv for plain chest radiograph).⁸⁸⁻⁹⁰

CONCLUSION

The radionuclide renal study is only one method to supply renal structure, urodynamics in urinary collecting system and renal function in one test. In Japan, it was performed as one of the major examinations in routine nuclear medicine but is decreasing in number now. I wonder where it is going in the new century in Japan. Woolfson et al.⁹¹ described that "much of the progress in renal nuclear medicine has been driven by technological development,

but without rigorous assessment the value of some of these studies has been overestimated. The only tests to achieve gold standard status are the isotopic GFR, the DMSA renogram to detect cortical abnormalities and the captopril renogram when used to define those hypertensive patients who will not benefit from renovascular intervention. Consensus guidelines must be followed and routine protocols for combination tests must be developed, but even so isotopic renography is likely to be overtaken by competing technologies which can provide one test to give simultaneous information about both structure and function." Their comments may be true, but I do not think that the clinical utilization of radionuclide renal study has reached the maximum state in Japan. A concept of TER obtained by ^{99m}Tc-MAG3 study is not familiar to most clinicians. Russell and Dubovsky of the University of Alabama at Birmingham⁶⁸ describe that such problems have been resolved by education of students, residents and physicians in the institution. In order to maintain such circumstances in Japan, we have to learn

Table 6 Comparison of radiopharmaceutical and clinical properties between ^{99m}Tc -MAG3 and ^{99m}Tc -DTPA in routine practice

Properties	^{99m}Tc -MAG3	^{99m}Tc -DTPA
Renal function	plasma flow (ERPF) and tubular function (TER)	glomerular function (GFR)
Extraction efficiency	68%	20%
Protein binding	about 90%	< 5–10%
Urinary excretion	about 70%/injected dose (30 min)	about 20% (30 min), 45–65% (3 hr), 90% (24 hr)
Quantification	single-plasma sample	single- or 2-plasma sample
sampling time	40–45 for adults 35 min for children	180–240 min for adults 120 min for children
Image quality	excellent	good
Diseases		
RVH	equal to or better than ^{99m}Tc -DTPA	theoretically better than ^{99m}Tc -MAG3
Hydronephrosis	excellent	limited in poor renal function
Renal transplant	excellent	good
Acute renal failure	excellent, prognostic indicator (?)	good, perfusion image essential
Chronic renal failure	good, sensitive to decreased renal blood flow	quantitatively common to preserved renal function
Urinary leak	excellent	good

from their many achievements so far, that we should try to always give quantitative estimates in routine study, which is accurate, reliable and universally applicable. Of course, a new radiopharmaceutical is very important in the progress of renal nuclear medicine.⁹²

I would like to close this paper with comments by Levey,⁹³ that “estimation of GFR from renal clearance of radioisotope-labeled filtration markers, using a bolus infusion and spontaneous bladder emptying, is accurate, precise, and more convenient than the classical inulin clearance technique, and that measurements of GFR should be included both in clinical practice and in clinical research.” His comments must be also suited to TER using ^{99m}Tc -MAG3 at present and in future (Table 6).⁹⁴

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