Estimation of Technetium-99m-MAG_3 Renal Clearance in Children: Two Gamma Camera Techniques Compared with Multiple Plasma Samples

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Dynamic renal scintigraphy using technetium-99m mercaptoacetylglycylglycylglycine (MAG_3) has been described in adults, and clearance values have been established using mutliple plasma samples. This study of renal clearance has compared two fundamentally different gamma camera techniques (both of which require a single blood sample) with the multiple blood sampling technique in children (n = 30). Results show that a 40-min dynamic ^{99m}Tc-MAG_3 renal scintigram coupled with a single plasma sample will allow analysis of the data so that clearance values, which are similar to those from multiple plasma samples, may be calculated. The curve generated from the cardiac region of interest (ROI) provided clearances values that had a high correlation coefficient (0.939–0.951) compared to the multiple-plasma sample technique immaterial of the timing of the blood sample. The renal uptake method of clearance had a lower correlation coefficient (0.89–0.92), which varied with the timing of the blood sample compared to the multiple-plasma sampling technique. This study has demonstrated that an extended gamma camera acquisition coupled with a single-plasma sample may be used for quantitative renal function studies using ^{99m}Tc-MAG_3.

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The introduction of ^{99m}Tc-MAG_3 into adult nephrourology has resulted in the availability of a ^{99m}Tc-labeled tracer with a high renal extraction. The need to provide absolute quantification of the clearance of this isotope has been described in adults (*1–3*). The value of this isotope in children is related to its favorable dosimetry (*4*) and its low background, 40–60 min after the study, allowing indirect radionuclide cystography to be performed (*5*). In children, the kidney is maturing and therefore one should distinguish between deterioration of one kidney and maturation of the other (normal) kidney. Absolute clearance values of ^{99m}Tc-MAG_3 [the tubular excretion rate (TER)] are required in pediatrics. Multiple plasma samples are not feasible in children, especially in the young, therefore a technique is required in which TER can be calculated using a single-plasma sample. Tauxe has suggested a formula to calculate absolute clearance in children, but this is based on certain assumptions and empirical observations (*6*). This study compares renal clearance using multiple plasma samples in children against two gamma camera techniques during renography; the renal uptake method and the cardiac disappearance method. Each technique offers the possibility of routine estimation of absolute ^{99m}Tc-MAG_3 clearance in children from a single-plasma sample.

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PATIENTS AND METHODS

Thirty children were referred for dynamic ^{99m}Tc-MAG_3 renal scintigraphy and indirect radionuclide cystography. Patient data are listed in Table 1. Fourteen children had evidence of impaired renal function, as judged by either a GFR <50 ml/min/1.73 m^2 or a serum creatinine >150 μmol/liter. All children were well hydrated orally 20 min prior to intravenous injection of ^{99m}Tc-MAG_3 (the dose was on body weight calculated from an adult dose of 80 MBq/70 kg).

Multiple Plasma Samples

A second intravenous line was inserted at the start of the study and 2 ml of blood were drawn at approximately 10, 15, 20, 30, 40, and 50 min in all children. At the drawing of each blood sample, 2 ml of blood were withdrawn before the actual sample was taken. This original 2 ml was then reinjected into the child. Each sample was centrifuged for 5 min, activity in 0.2 ml of plasma was measured in a well counter as well as the same volume of a standard noting the time of measurement. From the six plasma samples, a double-exponential was calculated by computer using an iterative process. The clearance was then derived from the method of Sapirstein (*7*). This clearance was used to compare the two other clearance techniques.

Gamma Camera Studies

Dynamic scans were acquired for 40 min on a large field of view gamma camera linked to a dedicated nuclear medicine computer in a 128 × 128 matrix with the child supine. The full syringe as well as the empty syringe connecting tubing and needle

TABLE 1
Patient Data

Patient No.	Sex	Age (yr)	Height (cm)	Weight (kg)	S.A. m^2	
1	M	6.6	114	17	0.742	*
2	M	13.10	172	53	1.62	
3	F	8.8	125	24	0.918	
4	F	3.	157	47	1.44	
5	F	7.5	120	22	0.859	*
6	F	15.4	158	65	1.66	
7	M	5.7	115	24	0.864	*
8	M	8.3	125	26	0.95	
9	M	8.9	135	30	1.07	*
10	M	12.11	149	41	1.31	
11	F	8.10	131	27	0.999	
12	M	12.1	140	31	1.12	*
13	F	9.6	146	35	1.21	*
14	F	8.8	139	31	1.11	
15	M	13.5	165	55	1.60	
16	F	9.3	124	25	0.929	
17	F	9.7	133	28	1.03	
18	M	9.11	126	20	0.855	*
19	M	9.5	132	24	0.955	
20	F	9.6	125	21	0.868	*
21	F	7.3	119	24	0.886	*
22	F	14.11	158	52	1.51	
23	F	11.9	153	61	1.58	
24	F	13.3	169	60	1.69	
25	M	7.4	120	15	0.73	*
28	M	12.6	157	44	1.40	*
29	M	10.3	155	50	1.47	
30	M	5.7	104	15	0.658	*
29	M	6.8	105	19	0.733	*
30	M	5.4	115	21	0.817	*

* Impaired renal function.

were counted on the face of the gamma camera. All acquisition times were automatically stored by the computer. Regions of interest (ROI) were placed around each kidney and the heart. Perirenal background ROIs (two pixels larger than the renal ROI) were automatically generated by the computer. Curves of 60-sec frame rate were generated from all five ROIs over the 40-min study. Fitted curves were extrapolated to 50 min.

Gamma Camera Renal Clearance

During the period up to 140 sec following mixing, the activity in the kidney reflected clearance of ^{99m}Tc-MAG_3, since no isotope had left the kidney. If the background subtracted renal curve is divided by the cardiac curve and plotted against the integral of the cardiac curve divided by the cardiac curve (Patlac plot), then a straight line results during clearance time and before the isotope leaves the kidney (*8*). The slope of this straight line reflects renal clearance. Therefore, taking a plasma sample allows the cardiac curve to be expressed in cts/per ml of plasma. Depth correction for attenuation is made based on the body weight using the formula 2.028 + 0.0742 × Wt (kg) (*9*), so that individual kidney ^{99m}Tc-MAG_3 clearance could be calculated for each plasma sample taken. The values for the two kidneys were added to give global clearance. Five clearance values were obtained for each child (R1 = 10 min, R2 = 20 min, R3 = 30 min, R4 = 40 min, and R5 = 50 min samples).

Gamma Camera Cardiac Clearance

A double-exponential was iteratively fitted to the 4–40 min cardiac curve. Using each plasma sample, this curve was converted from counts/frame to cps/ml. The clearance was calculated in the same manner as for the multiple plasma samples. Five clearance values were obtained for each child, one for each plasma sample (H1 = 10 min, H2 = 20 min, H3 = 30 min, H4 = 40 min, H5 = 50 min samples).

Linear regression analysis was used to analyze the data.

RESULTS

Multiple-Plasma Sample Technique

Clearance from the plasma disappearance curve was calculated using the formula:

$$Cl = \frac{D \times \Lambda_1 \times \Lambda_2}{(A \times \Lambda_2) + (B \times \Lambda_1)},$$

where Λ_1 = decay constant of the first exponential; Λ_2 = decay constant of the second exponential; A = Y intercept of the first exponential; B = Y intercept of the second exponential; and D = the injected dose.

Clearance from the six plasma samples is shown in Table 2. Renal clearance from the uptake method was calculated using the formula:

$$Cl = \frac{\frac{dR}{dt}}{P},$$

where dR is the change in renal activity with time dt and P is the plasma concentration at time T. Integration of above equation and dividing each side by P gives the Patlac plot.

$$Cl = \frac{R(t)/P(t)}{\int P(t)/P(t)}$$

The slope of this curve between 60–140 sec (i.e., under conditions when no tracer is leaving the kidney) represents renal clearance in which a blood sample allows the conversion of the cardiac curve to counts/frame/ml.

Global renal clearance from the uptake method and cardiac clearance was calculated for each plasma sample, resulting in five clearance values per child (see Table 2). The comparison between clearance as measured by multiple plasma samples and both the renal uptake method and the cardiac ROI have been calculated separately for each timed plasma sample (Table 3). Using 95% confidence limits and 95% prediction limits for the linear regression analysis, the intercept for the renal uptake method compared to the multiple-plasma sampling method varied from 15.0% to 21.7%. The slope varied from 1.15 to 1.36. Figure 1 shows the best fit using the 10-min blood sample. The intercept for the cardiac ROI method compared to the multiple-plasma sampling method varied from 14.6% to 19.68%. This was significant at the 5% level. The slope varied from 0.89% to 1.05%. Figure 2 shows the best fit using the 40-min blood sample.

TABLE 2
Clearance Estimation on 30 Children

Patient no.	M	Cardiac ROI clearance					Kidney Uptake clearance				
		H1	H2	H3	H4	H5	K1	K2	K3	K4	K5
1	76	71	77	83	85	83	96	104	112	115	113
2	185	206	218	193	205	192	272	292	259	275	257
3	168	199	220	242	220	192	196	216	238	216	188
4	209	212	270	265	231	185	315	402	395	344	276
5	95	111	121	135	134	116	138	150	168	167	145
6	221	228	285	282	264	232	301	377	373	349	307
7	60	143	136	171	173	155	178	170	214	216	194
8	126	133	155	154	155	138	174	202	201	203	180
9	19	46	50	49	47	44	27	29	29	27	25
10	164	158	171	183	187	178	193	208	223	221	217
11	142	138	151	157	156	139	171	187	195	193	173
12	98	108	112	114	112	102	119	124	126	124	113
13	92	89	96	109	111	108	98	106	120	121	118
14	216	201	211	213	215	247	220	231	234	236	271
15	159	106	120	140	165	186	209	237	277	325	367
16	100	115	139	138	120	97	135	164	162	141	114
17	128	123	132	142	145	153	172	184	198	202	213
18	97	86	106	115	126	120	118	145	157	1721	164
19	141	136	151	169	183	191	175	193	217	235	245
20	24	86	88	94	92	90	114	116	125	122	119
21	90	87	104	101	108	96	109	130	125	135	120
22	283	275	300	319	344	313	335	366	390	420	383
23	202	198	219	222	211	189	213	234	237	226	202
24	164	167	186	195	203	190	284	316	332	345	323
25	86	99	108	111	102	82	109	119	123	113	91
26	51	45	50	56	57	58	45	50	56	57	59
27	250	217	250	266	278	273	267	308	328	343	337
28	11	1	1	1	1	1	16	17	18	19	20
29	18	17	18	18	19	19	8	8	8	9	8
30	22	5	5	5	5	5	16	16	16	17	0.17

M = Multiple-plasma sample technique; H1 = cardiac ROI clearance with plasma sample at 10 min; H2 = cardiac ROI clearance with plasma sample at 20 min; H3 = cardiac ROI clearance with plasma sample at 30 min; H4 = cardiac ROI clearance with plasma sample at 40 min; H5 = cardiac ROI clearance with plasma sample at 50 min; K1 = kidney uptake clearance with plasma sample at 10 min; K2 = kidney uptake clearance with plasma sample at 20 min; K3 = kidney uptake clearance with plasma sample at 30 min; K4 = kidney uptake clearance with plasma sample at 40 min; and K5 = kidney uptake clearance with plasma sample at 50 min.

DISCUSSION

Multiple-plasma sample testing to observe plasma disappearance over an appropriate time period is the accepted method for calculating renal clearance following a single injection of a hippuran or ^{99m}Tc-MAG$_3$ (*10*). In routine clinical practice, a single-plasma sample technique would be preferable especially in children (*6*). Techniques have

TABLE 3
Correlation Between Multiple-Plasma Sample and both Cardiac ROI and Renal Uptake Clearance Values

	Time of blood sample in minutes				
	10	20	30	40	50
Cardiac ROI Clearance					
Intercept	17.1	14.6	19.7	18.7	16.9
P against 0	0.06	0.135	0.07	0.05	0.07
Slope	0.89	1.03	1.04	1.05	0.99
P against 0	0.00000	0.00000	0.00000	0.00000	0.00000
Renal Uptake Clearance					
Intercept	18.9	15.03	21.74	21.4	20.3
P against 0	0.15	0.34	0.19	0.21	0.25
Slope	1.15	1.34	1.35	1.36	1.28
P against 0	0.00000	0.00000	0.00000	0.00000	0.00000

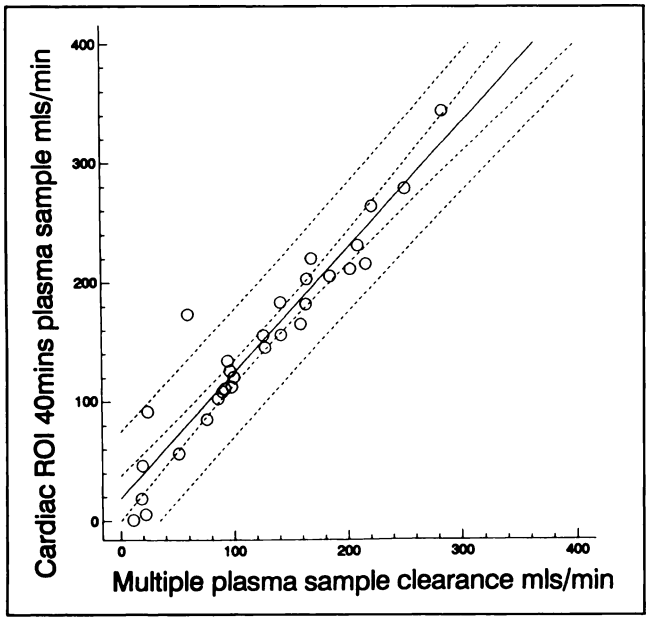

FIGURE 1. Linear regression of renal clearance uptake using the 10-min plasma sample method on clearance with multiple plasma sampling. Intercept = 18.9; Probability level = 15%; Slope = 1.15; Probability level = 0.0000; Correlation coefficient = 0.924; and R^2 = 85.34%.

been proposed where no plasma sample is taken. In children, where there is a changing volume of distribution with age, especially in the infant, the assumptions necessary for calculation of clearance may not be valid using

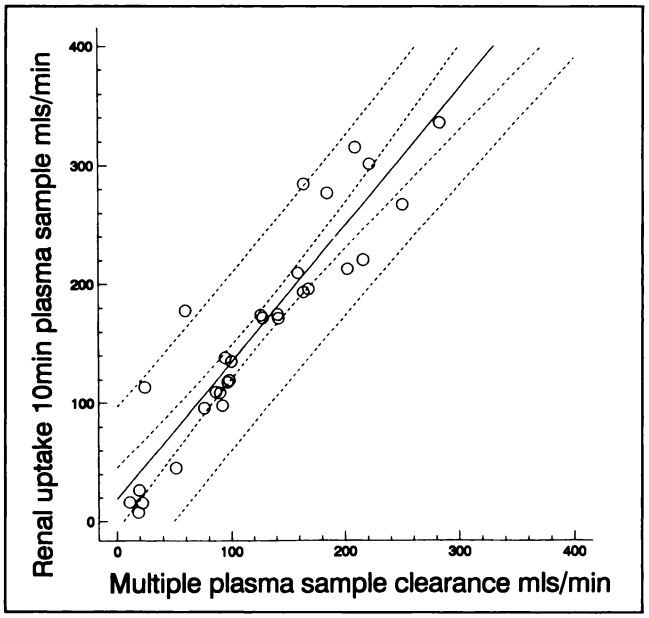

FIGURE 2. Linear regression of cardiac ROI clearance using the 40-min plasma sample method on clearance with multiple plasma sampling. Intercept = 18.69; Probability level = 5%; Slope = 1.05; Probability level = 0.0000; Correlation coefficient = 0.951; and R^2 = 90.36%.

^{99m}Tc-MAG$_3$ with a higher protein binding than hippuran and a lower renal extraction fraction.

The technique of measuring renal clearance by studying renal uptake was described by Piepsz et al. (*11*) using ^{99m}Tc-DTPA. This technique was validated at this institution in children with a single kidney by Vivian et al. (*12*) and in an experimental situation by Kelleher (personal communication). The principle applies to any tracer that is dynamically excreted by the kidney. The analysis of the renogram is made prior to the isotope entering the renal pelvis (i.e., before 120–140 sec), then the amount of isotope excreted by the kidney will reflect clearance of this isotope by the kidney. Background subtraction must be applied (*13*) so that the measured activity over the kidney approximates true renal activity. Using the Patlac plot popularized by Rutland (*8*), a robust parameter may be used to observe the renal curve during this short time period. The advantage of this method is that only a single plasma sample is required. The results of this study show that there is a high correlation coefficient between the renal uptake method compared to the multiple-plasma sample technique with a significant R^2 value that appears to be independent of the timing of the plasma sample.

The blood disappearance curve using the gamma camera and a ROI over the heart has theoretical disadvantages since this curve will be "contaminated" by both the small amount (5%) of ^{99m}Tc-MAG$_3$ in the red blood cells (*14*) as well as the extravascular ^{99m}Tc-MAG$_3$. The plasma protein binding of ^{99m}Tc-MAG$_3$ is reported to be 90% in man (*15*), suggesting that this latter effect may be minimal. The results presented in this study suggest that the fitted curve from the cardiac ROI with a prolonged gamma camera study shows a high correlation coefficient between the cardiac ROI method compared to the multiple-plasma sample technique with a significant R^2 value that appears to be independent of the timing of the plasma sample. The intercept of the linear regression analysis is significantly different from zero at the 5% level, suggesting that the cardiac ROI technique will systematically overestimate clearance compared to the multiple-plasma sample technique. This may be due to the small amount of free ^{99m}Tc-MAG$_3$ which will add to the activity recorded by the cardiac ROI technique and the "contamination" of the cardiac ROI by ^{99m}Tc-MAG$_3$. This study has shown that using a single plasma sample and either the cardiac ROI technique during a prolonged gamma camera study or the renal uptake method will provide clinically accurate results of clearance for ^{99m}Tc-MAG$_3$ in children.

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