Technetium-99m-MAG_3 Versus Iodine-123-OIH: Renal Clearance and Distribution Volume as Measured by a Constant Infusion Technique

Johan A. C. Prenen,* John M. H. de Klerk, Alfred D. van het Schip, and Peter P. van Rijk

Department of Nuclear Medicine, University Hospital Utrecht, Heidelberglaan, Utrecht, The Netherlands

The renal clearance and distribution volume of ^{99m}Tc-mercaptoacetyltriglycine (MAG_3) and ^{123}I-o-iodohippurate (OIH) were determined separately in six normal male volunteers using the constant infusion clearance technique in order to validate single injection clearance techniques and subsequently the normal values for these parameters. MAG_3 renal clearance was 257 ± 24 ml/min/1.73 m^2, compared to the OIH clearance of 556 ± 46 ml/min/1.73 m^2 resulting in a MAG_3/OIH clearance ratio of 0.47 ± 0.06. The MAG_3 and OIH apparent distribution volumes at steady-state were 14.8 ± 3.7 and 19.4 ± 5.3 liters, respectively, the latter value approximating the extra cellular fluid volume. Urinary excretion in the 0–30-min period after intravenous administration was 64.4 and 70.2% for MAG_3 and OIH, respectively. This investigation revealed some significant differences in the normal values of the renal clearance and distribution volume of MAG_3 compared with other studies.

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At present, ^{123}I-o-iodohippurate (OIH) has been largely replaced by the radiopharmaceutical ^{99m}Tc-mercaptoacetyltriglycine (MAG_3) for renographic studies due to the excellent scintigraphic imaging qualities of this compound. Knowledge of the renal clearance and distribution volume of MAG_3 is indispensable for a better understanding of its renal handling. In recent studies, wide variations in absolute values for the clearance and distribution volume of MAG_3 have been reported (*1–3*).

The classical constant infusion clearance technique permits precise measurement of the renal clearance of an appropriate compound and consequently this method is pre-eminently suitable in the validation of other clearance techniques (*4,5*).

In the present study renal clearance, total clearance, and apparent distribution volume at steady-state of both MAG_3 and OIH was assessed by the constant infusion clearance technique in normal subjects.

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For reprints contact: J.A.C. Prenen, MD, PhD, Dept. of Nuclear Medicine, St. Franciscus Ziekenhuis, Boerhaavelaan 25, 4708 AE Roosendaal, The Netherlands.

* Present address: Department of Nuclear Medicine, St. Franciscus Ziekenhuis, Boerhaavelaan 25, 4708 AE Roosendaal, The Netherlands.

MATERIALS AND METHODS

Subjects

In six normal male volunteers (age 23–30 yr), the renal clearance of MAG_3 and OIH was determined separately within a 7-day period by means of the constant infusion technique with urine collection. Height and weight were measured in order to normalize the data to body surface area (*6*). Informed consent was obtained from all the persons participating in this study. The protocol was approved by the Committee on Ethics of the Utrecht University Hospital.

Radiopharmaceuticals

Technetium-99m-mercaptoacetyltriglycine was prepared from a lyophilized kit (TechneScan MAG_3; Mallinckrodt Diagnostica BV, Petten, The Netherlands) according to the manufacturer's instructions and injected within 1 hr of preparation. The radiochemical purity of MAG_3 was measured by high-performance liquid chromatography (HPLC) and found to be consistently >97% for at least 6 hr after reconstitution of the kit as we (*7*) and others (*8,9*) reported elsewhere. Sodium ^{123}I-o-iodohippurate (Hippuran, purity 99%) was purchased from Cygne, Eindhoven, The Netherlands and diluted as necessary for use.

MAG_3 and OIH Clearance

After a bolus intravenous priming dose (±s.d.) of 99.1 ± 8.4 MBq of MAG_3, a constant infusion containing approximately 3.0 MBq/ml of MAG_3 was started at a rate of 10 ml/hr: the total infusion period was 3 hr. The priming dose of OIH (±s.d.) amounted to 23.1 ± 2.0 MBq, whereas the constant infusion solution contained approximately 0.7 MBq/ml of OIH. By this approach, a constant level of both MAG_3 and OIH was reached about 90 min after the start of the infusion (equilibrium time) and was maintained for 90 min. Blood samples drawn at 5-, 10- and 15-min intervals in the 0–30-, 30–120-, and 120–180-min periods, respectively, were collected in heparinized syringes and centrifuged immediately upon collection. Urine was collected at 30-min intervals by spontaneous voiding. Adequate diuresis was ensured by regular fluid intake, amounting to 3 liters from 1 hr prior to and for the duration of the study.

Radioactivity Measurement

Radioactive assay of the plasma (0.25 ml) and urine (0.25 ml) samples was performed in duplicate in a Minaxi gamma counter. Appropriate corrections were made for decay. Counting of the priming dose as well as the constant infusion solution was included.

Endogenous Creatinine Clearance

For two days preceding the infusion studies (subjects were ambulant), 24-hr urine samples were collected for determination of creatinine, and blood samples were taken for determination of the serum creatinine level in order to calculate the endogenous clearance of creatinine (*10*).

Calculation of Pharmacokinetic Parameters

The constant infusion technique with urine collection permits calculation of the relevant pharmacokinetic parameters when, after an appropriate loading dose followed by an appropriate maintenance infusion dose, constant plasma concentrations have been established (*11,12*).

Total-Body Plasma Clearance (Cl_{tot}). Cl_{tot} of MAG_3 and OIH was calculated according to Gibaldi and Perrier (*12*):

$$Cl_{tot} = \frac{D_{in;t_1 \rightarrow t_2}}{AUC_{t_1 \rightarrow t_2}} \text{ (ml/min)},$$

in which $D_{in;t_1 \rightarrow t_2}$ (cpm) is the dose administered between the specified time points when equilibrium has been established (steady-state situation) and $AUC_{t1 \rightarrow t2}$ (min × cpm/ml) is the area under the plasma-concentration versus time curve for the same period at steady-state. The 2–3-hr interval after starting was taken from the time when 2-hr steady-state conditions were attained. This was confirmed by analysis of the 120-, 135-, 150-, 165- and 180-min plasma samples, showing a constant concentration for both MAG_3 and OIH (see Fig. 1). Calculation of $AUC_{t1 \rightarrow t2}$ was accomplished by use of the trapezoidal rule. The endogenous clearance of creatinine was calculated by the standard formula.

Renal Plasma Clearance (Cl_{ren}). Cl_{ren} was calculated according to Gibaldi and Perrier (*12*):

$$Cl_{ren} = \frac{A_{urine;t_1 \rightarrow t_2}}{AUC_{t_1 \rightarrow t_2}} \text{ (ml/min)},$$

where $A_{urine;t1 \rightarrow t2}$ (cpm) is the amount excreted into urine during a specified interval at steady-state which was the same as for the Cl_{tot} calculation.

Apparent Volume of Distribution at Steady-State ($V_{d,ss}$). Under steady-state conditions, $V_{d,ss}$ (the parameter relating the actual amount in the body to the plasma concentration) can be calculated from:

$$V_{d,ss} = \frac{D_{in;0 \rightarrow t} - D_{out;0 \rightarrow t}}{C_{avg;ss}} \text{ (ml)},$$

where $D_{in;0 \rightarrow t}$ (cpm) is the sum of loading dose and maintenance dose infused up to time of calculation and $D_{out;0 \rightarrow t}$ (cpm) is dose eliminated from the body up to that time which equals dose excreted into urine up to that time. The latter only applies when $Cl_{tot} = Cl_{ren}$, which is applicable to both MAG_3 and OIH (see Results). $C_{avg;ss}$ is the mean plasma radioactivity concentration (cpm/ml) at steady-state (i.e., the mean value of the concentrations at 120, 135, 150, 165 and 180 min, respectively).

Plasma Protein Binding

MAG_3 and OIH plasma-protein binding were determined by centrifugal ultrafiltration using the Amicon Centrifree micropartition system (*13*).

Statistical Analysis

Significance of differences was determined using the Student's paired t-test.

RESULTS

In Figure 1, the MAG_3 and OIH plasma radioactivity pattern is shown in a typical study in the same normal subject. The results of the renal clearances of MAG_3, OIH and creatinine (±s.d.) normalized to body surface area are presented in Table 1. For the creatinine clearance values we used the mean of four clearance calculations in each subject. The MAG_3-to-OIH clearance ratio (±s.d.) was found to be 0.47 ± 0.06.

In Table 2 the clearance values of MAG_3 and OIH as calculated with (Cl_{ren}) and without (Cl_{tot}) urine collection are presented. The mean values for the MAG_3 renal and total clearance (±s.d.) were nearly identical: 257 ± 24 and 268 ± 35 ml/min/1.73 m^2, respectively ($p < 0.05$).

The mean OIH renal and total clearance values (±s.d.) were also in close agreement viz 556 ± 46 and 529 ± 81 ml/min/1.73 m^2, respectively ($p < 0.05$). The values of the $V_{d,ss}$ of MAG_3 and OIH are presented in Table 3. The $V_{d,ss}$ ratio of MAG_3-to-OIH (±s.d.) was found to be 0.74 ± 0.17. In Table 4 the amount of MAG_3 and OIH excreted in the 0–30 min period of the study has been expressed as a percentage of the total dose of radioactivity administered (excretion fraction). The values of the excretion fraction of MAG_3 as compared to OIH were found to be of the same order of magnitude.

In Figure 2, an example of the HPLC profile of the radioactivity in the urine is presented in an overlay plot for comparison with the profile of a typical preparation of MAG_3, indicating that MAG_3 is excreted without being metabolized.

Table 5 shows the values of the plasma half-lives of MAG_3 and OIH as calculated from the slow component

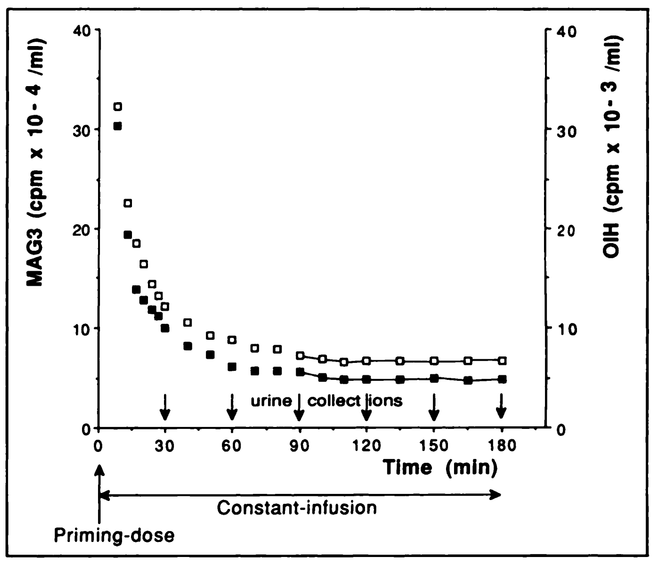

FIGURE 1. Plasma radioactivity pattern of both MAG_3 (□—□) and OIH (■—■) in the same subject.

TABLE 1
Renal Clearance of MAG_3, OIH, and Endogenous Creatinine Normalized to Body Surface Area

Subject no.	Height (m)	Weight (kg)	Clearance (ml/min/1.73 m^2) MAG3	OIH	Creatinine	Clearance ratio MAG3/OIH
1	1.90	78	232	516	97	0.45
2	1.83	77	223	640	116	0.35
3	1.91	84	261	550	132	0.47
4	1.93	85	272	513	107	0.53
5	1.74	74	270	553	112	0.49
6	1.85	75	285	562	121	0.51
mean			257	556	114	0.47
s.d.			24	46	12	0.06

TABLE 3
Apparent Distribution Volume at Steady-State ($V_{d,ss}$) of MAG_3 and OIH Normalized to Body Surface Area

Subject no.	$V_{d,ss}$ (liter/1.73 m^2) MAG3	OIH	$V_{d,ss}$-ratio MAG3/OIH
1	16.3	22.5	0.72
2	17.5	28.1	0.62
3	9.7	18.3	0.53
4	12.2	14.1	0.86
5	—	14.1	—
6	18.2	19.2	0.95
mean	14.8	19.4	0.74
s.d.	3.7	5.3	0.17

MAG_3 and OIH as calculated from the slow component of the plasma radioactivity disappearance curve in the 0–30 min period. The mean values (±s.d.) were nearly identical ($p < 0.05$). In addition, plasma-protein binding of MAG_3 and OIH as measured by centrifugal ultrafiltration (±s.d.) was found to be 88.1 ± 3.8 (53 measurements) and 67.9% ± 4.0% (42 measurements), respectively.

DISCUSSION

Renal handling of OIH is comprehensively understood as opposed to MAG_3. Studies of MAG_3 in humans (*1*) and in rats (*14*) indicate that nonrenal loss does not play an appreciable role in its excretion pattern. This is confirmed by our findings that show no significant difference between renal and total-body clearance of MAG_3, indicating that its excretion by organs other than the kidney is negligible in normal subjects. In addition, we found by HPLC chromatography that the radioactivity in the urine was present exclusively as MAG_3 in accordance with previously published data (*9*). These findings imply that MAG_3 has to be considered as an appropriate compound for the determination of its renal clearance.

In the present study, we applied the constant infusion technique for MAG_3 and OIH because it permits determination of both the renal clearance and $V_{d,ss}$ accurately and independently from each other (*11*). Since $Cl_{ren} = Cl_{tot}$ as we have shown above, potential errors in the calculation of $V_{d,ss}$ due to disturbing effects of dead space in the urinary tract can be considered insignificant.

Our mean value (±s.d.) for OIH clearance (556 ± 46 ml/min/1.73 m^2) approximates the generally accepted 600 ml/min for effective renal plasma flow (ERPF) in normal subjects, measured as the paraaminohippuric acid (PAH) clearance. The OIH/PAH clearance ratio has been reported to be 0.87 (*15*). Estimation of the extra cellular fluid volume (ECFV) from height, weight and sex in our subjects revealed a mean value (±s.d.) of 18.9 ± 1.8 liters (*16*), which is of the same order of magnitude as the $V_{d,ss}$ for OIH reported in the present study: 19.4 ± 5.3 liters. Taylor et al. (*1*) found a MAG_3 plasma clearance (±s.d.) of 288 ± 53 ml/min/1.73 m^2 in normal volunteers, whereas for the volume of distribution a value (±s.d.) of 4.4 ± 0.8 liters was reported. As compared to our study the value for the MAG_3 clearance was of the same order of magnitude (257 ± 24 ml/min/1.73 m^2), but for the MAG_3 distribution volume we found an evidently higher value viz 14.8 ± 3.7 liters. In the present study, the MAG_3/OIH clearance ratio (±s.d.) was found to be 0.47 ± 0.06, whereas Jafri et al. (*2*) reported a value (±s.d.) of 0.61 ±

TABLE 2
MAG_3 and OIH Clearance Normalized to Body Surface Area, Calculated with (Cl_{ren}) and Without (Cl_{tot}) Urine Collection

Subject no.	Clearance (ml/min/1.73 m^2) MAG3 Cl_{ren}	MAG3 Cl_{tot}	OIH Cl_{ren}	OIH Cl_{tot}
1	232	214	516	544
2	223	243	640	676
3	261	261	550	489
4	272	287	513	434
5	270	307	553	519
6	285	294	562	514
mean	257	268	556	529
s.d.	24	35	46	81

TABLE 4
Urinary Radioactivity Excreted in the 0–30-Min Period Expressed as a Percentage of the Total Dose Administered (Excretion Fraction)

Subject no.	MAG3 (%)	OIH (%)
1	66.7	73.8
2	57.7	75.1
3	65.0	69.2
4	65.9	55.4
5	67.9	78.0
6	63.4	70.0
mean	64.4	70.2
s.d.	3.6	8.0

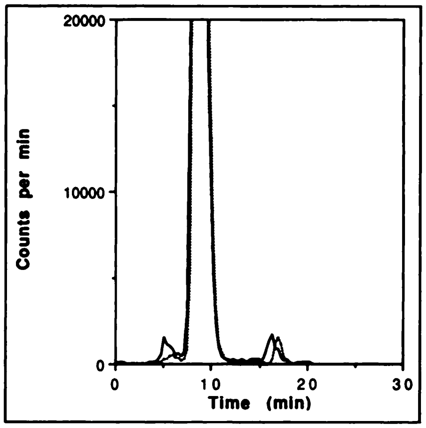

FIGURE 2. HPLC analysis of urine (···) compared to a typical preparation of MAG_3 (—).

0.08 in patients with renal disorders, a value appreciably higher.

Furthermore, we found a substantially lower value (about 30%) for the normal MAG_3 clearance as compared to Russell et al. who suggested a value of 370 ml/min. All mentioned discrepancies might be due to methodologic differences, since these authors applied single injection clearance techniques in their investigations. Overestimation of the renal clearance of an indicator using single injection clearance techniques is well-known (*5,17*). The plasma-protein binding of MAG_3 was found to be significantly higher than that of OIH ($p < 0.01$), which is reflected in its considerably lower $V_{d,ss}$ with MAG_3/OIH ratio of 0.74 ± 0.17 (Table 3).

Despite the striking differences in renal clearance and distribution volume of MAG_3 as compared to OIH in the present study, extraction and excretion by the kidneys of both radiopharmaceuticals occur in almost equal proportions up to 30 min after intravenous injection (64.4% and 70.2%, respectively).

This phenomenon provides optimal renal imaging facilities for the ^{99m}Tc-labeled MAG_3 and as a consequence it appears to be an excellent substitute for OIH. It is clear, that precise measurement of basic parameters such as renal clearance and distribution volume are indispensable for a better understanding of renal handling of MAG_3, especially when clearance of MAG_3 will be used clinically as a measure for renal function.

In conclusion, application of the constant infusion clearance technique as described in this investigation, contributes to the validation of normal values of the renal clearance and distribution volume of MAG_3.

TABLE 5
Plasma Half-life of MAG_3 and OIH as Calculated from the Slow Component in the 0–30-min Period

Subject no.	Plasma half-life (min)	
	MAG_3	OIH
1	21.5	26.4
2	23.9	19.7
3	21.8	26.3
4	17.5	22.9
5	21.0	17.6
6	27.0	17.0
mean	22.1	21.7
s.d.	3.2	4.2

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