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# Comparison of Technetium-99m $MAG_3$ with Iodine-131 Hippuran by a Simultaneous Dual Channel Technique

Charles D. Russell, Brett Thorstad, Michael V. Yester, Marian Stutzman, Tim Baker, and Eva V. Dubovsky

*Division of Nuclear Medicine, University of Alabama Hospital, and, Nuclear Medicine Service, Birmingham V.A. Medical Center, Birmingham, Alabama*

Technetium-99m  $MAG_3$ , a technetium-labeled analog of hippuran, was compared with [ $^{131}I$ ] hippuran using a simultaneous dual isotope study in 20 patients. The plasma clearance for  $MAG_3$  was lower than that of hippuran, but its plasma concentration was higher, resulting in similar rates of excretion and similar renal time-activity curves. Apart from better statistics with the technetium-labeled agent, there were no clinically significant differences in this group of patients.

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The need for a renal agent with the desirable biologic properties of orthoiodohippurate (OIH, hippuran) but without the undesirable physical properties of iodine-131 ( $^{131}I$ ) has long been recognized. Orthoiodohippuran (OIH) is available with an iodine-123 ( $^{123}I$ ) label but the dose is limited by high price, the availability is limited by short half-life, and the image quality is limited by high energy emissions arising from both the decay of  $^{123}I$  itself and from radiochemical impurities. Recently, Taylor and others (1) reported that a new technetium chelate, technetium-99m ( $^{99m}Tc$ )  $MAG_3$ , had properties similar to OIH in a group of normal volunteers. The comparison used a laboratory preparation purified by high performance liquid chromatography. A readily prepared kit form is now under commercial development in the U.S. and also in another formulation in Europe (2). Here, we compared the U.S. kit formulation with simultaneously administered [ $^{131}I$ ]OIH in a group of 20 patients, using a dual channel technique both for imaging and blood clearance. No previous study has employed dual channel imaging to compare [ $^{99m}Tc$ ]  $MAG_3$  with [ $^{131}I$ ]OIH.

## METHODS

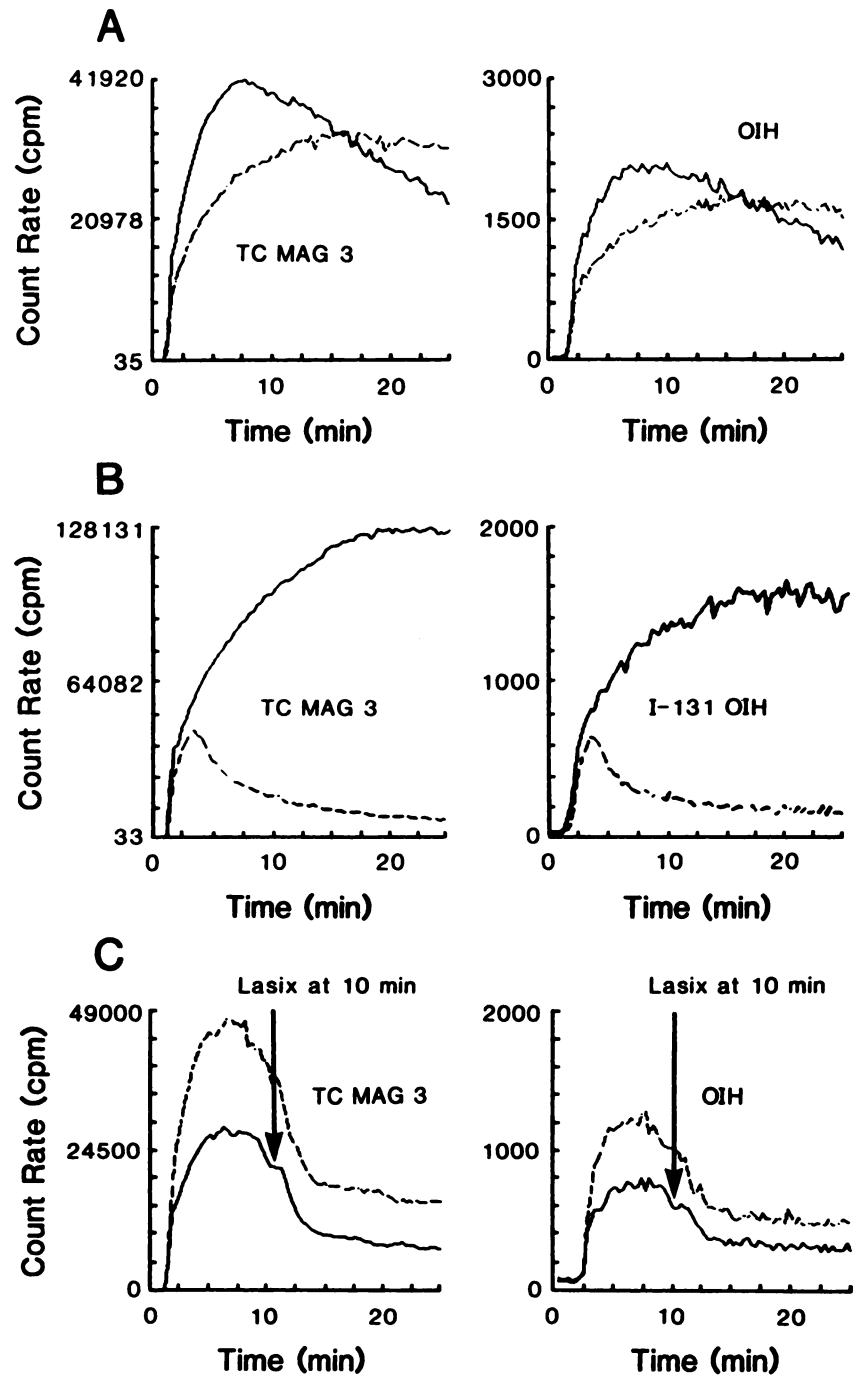
Twenty volunteers were recruited from adult patients referred to our clinic for radionuclide evaluation of renal function. Eleven had renal transplants and were imaged anteriorly. Of the remainder, three were referred for diuretic renograms to evaluate obstruction (0.5 mg/kg furosemide i.v. at 10 min) and two for angiotensin-converting enzyme inhibitor studies to evaluate hypertension (25 mg captopril p.o. 1 hr before study). These patients, and the remaining four, were imaged posteriorly. Urine collection was incomplete for three patients in one of which blood collection was also incomplete because of the failure of the heparin lock. In one case, the  $^{131}I$  camera data were inadvertently lost. The range of renal function in this population is displayed in Figure 4, in which OIH clearance can be interpreted as a close approximation to effective renal plasma flow (normally five times the glomerular filtration rate).

Simultaneous dual tracer studies were performed using 150  $\mu Ci$  of [ $^{131}I$ ]OIH per kidney and 5 to 10 mCi of [ $^{99m}Tc$ ]  $MAG_3$  per patient. Camera data were acquired for 27 min in 20-sec 64x64 pixel frames for separate  $^{99m}Tc$  and  $^{131}I$  windows using a high-energy collimator. Nine plasma samples were obtained between 4 and 90 min after injection and two urine samples were collected at 30 and 90 min. Plasma and urine specimens were counted with standards both for  $^{99m}Tc$  and  $^{131}I$ . Bladder images were obtained before and after each voiding to correct urine counts for residual bladder urine. The injection site was imaged in each case to exclude infiltration of the dose.

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For reprints contact: Charles D. Russell, MD, PhD, Div. of Nuclear Medicine, University of Alabama Hospital, 619-19th St. So., Birmingham, AL 35233.



**FIGURE 1**  
 Concurrent time-activity curves for  $^{99m}\text{Tc}$ MAG<sub>3</sub> and  $^{131}\text{I}$ OIH. A: Bilateral urinary retention related to neurogenic bladder with diversion procedure. B: Right renal artery stenosis (with ACE inhibitor). C: Bilateral urinary retention related to neurogenic bladder after diversion procedure, with diuretic administered 10 min after tracer injection (arrow).

#### DATA PROCESSING

For statistical analysis, the renal time-activity curves were corrected for decay and background using an annular background region of interest surrounding each kidney. Because the  $^{99m}\text{Tc}$  dose greatly exceeded that of  $^{131}\text{I}$ , spill-over from the  $^{131}\text{I}$  channel to the  $^{99m}\text{Tc}$  channel did not exceed 1% and was neglected. The injection time was taken as the first frame in which the count rate attained 5% of its maximum. Before determination of peak time and peak counts, a 1:2:1 smoothing algorithm was applied once. Blood and urine counts were corrected for background, decay, and spillover from the  $^{131}\text{I}$

into the  $^{99m}\text{Tc}$  channel. Urine counts were further corrected for postvoiding residual urine in the bladder, as determined from pre- and postvoiding bladder images. Doses were corrected for activity retained in the syringe as measured by dose calibrator. Clearances were calculated by dividing the total 90-min urinary excretion by the time integral of the plasma concentration:

$$\text{Clearance} = \text{urine activity} / \int_0^{90} (\text{plasma activity/ml}) dt$$

(This equation is derived by writing the differential mass balance equation for the kidney and integrating. Unlike methods based on plasma clearance alone, it does not require

extrapolation to infinite time nor the assumption that the kidneys are the sole route of excretion.)

## RESULTS

The fraction of administered dose found in the urine at 30 and 90 min was nearly identical for  $MAG_3$  and OIH: the slope of the regression line of  $MAG_3$  on OIH was 0.97 at 30 min and 1.00 at 90 min, with correlation coefficients 0.97 and 0.96, respectively. Similar findings were reported by Taylor (1) but expressed as population means. Regression analysis is more sensitive to small differences, since each patient is compared against himself.

Renal time-activity curves were also similar for the two agents, except for much better statistics with  $MAG_3$  (Fig. 1). The peak count rate per millicurie averaged 1.6 times higher with  $MAG_3$  than with OIH. Using 5 to 10 mCi of  $MAG_3$  versus 300  $\mu$ Ci of OIH, this gave 20 to 40 times as many clinically usable counts. The difference is apparent in the images (Fig. 2), even though the high-energy collimator and coarse pixel size used in this dual-isotope study do not do justice to the  $^{99m}Tc$  labeled agent. Renal time-activity curves were qualitatively similar (Fig. 1), but minor differences were apparent. Peak times agreed closely for those kidneys having well-defined peaks: the correlation coefficient was 0.94 and the regression slope did not differ significantly from identity. For normal kidneys (those with well-defined peak and normal ERPF), the washout phase of the renogram was shallower with  $MAG_3$  than with OIH; for impaired kidneys (those with poorly defined peak and diminished ERPF), the difference was less pronounced. This is illustrated in Figure 3, in which the steepness of the washout phase and peak quality are represented by the ratio of peak count rate to count rate at 20 min. The difference is less apparent when the data, as in Figure 1, are not corrected for decay. The difference in the slope of the washout phase did not affect clinical interpretation by conventional criteria.

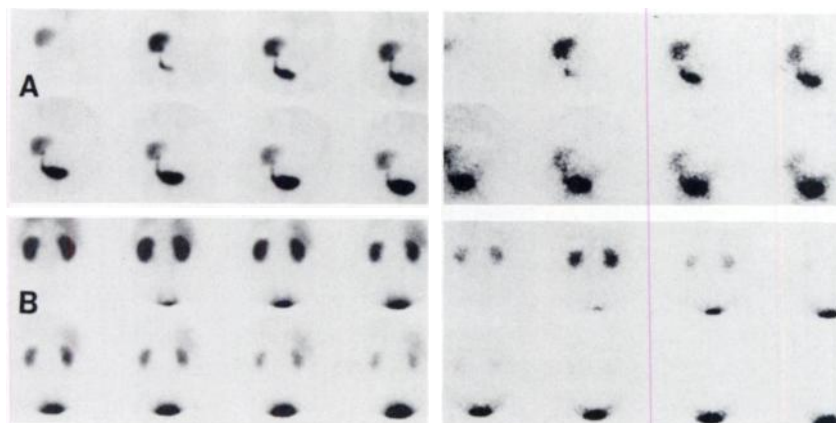
The most striking differences were in plasma clearance (Fig. 4) and plasma concentration (Fig. 5). The plasma clearance of  $MAG_3$  was only about one-half that of OIH ( $0.56 \pm 0.04$ , regression slope  $\pm$  s.d., but its plasma concentration was much higher (Fig. 5), in concordance with the protein binding and distribution volume data reported by Taylor (1). Since excretion is the product of plasma concentration times clearance, the two effects cancel, explaining the similar urinary excretion and similar time-activity curves.

Unlike OIH,  $MAG_3$  was found to be confined almost entirely to the plasma. The fraction of blood activity found in red cells in 41 samples obtained from seven of these patients was  $-0.003 \pm 0.001$  (the slight negative value being due to inexactness of the 4% correction for trapped plasma).

## DISCUSSION

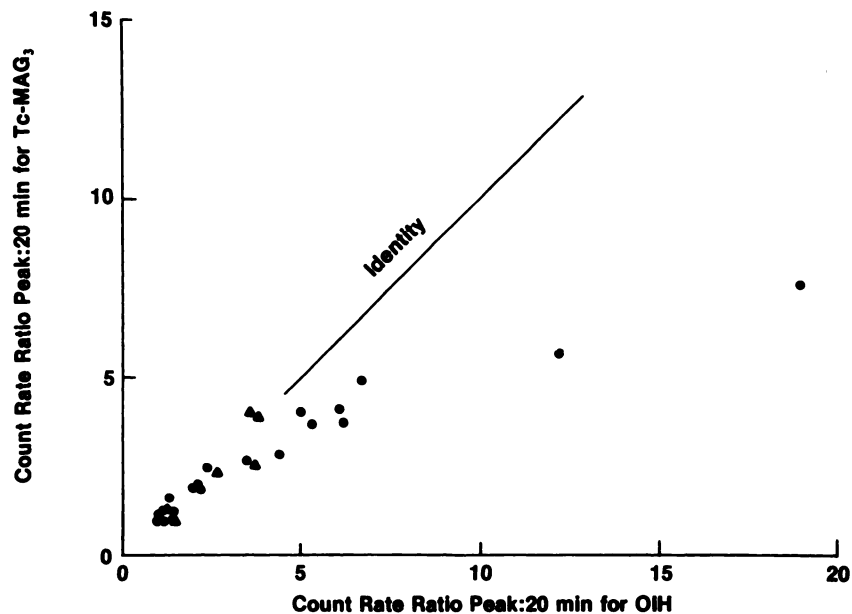
$MAG_3$  has biologic properties similar to OIH but with the more suitable energy and better dosimetry that go with a  $^{99m}Tc$  label. Now that low-energy isotopes dominate current practice, high-energy collimators of good quality are hard to find and most cameras have crystals too thin for good efficiency with  $^{131}I$  (3). Together with better statistics and lower radiation dose, these considerations favor the new agent.

In this study of 20 patients (including three diuretic studies and two studies with ACE inhibitors), no clinically important differences were found apart from the superior statistics of  $MAG_3$ . Small differences were seen, most notably in the washout slope of the renogram in normal kidneys. Because of its high extraction fraction, nearly 20% of an OIH dose is deposited during the first pass of the injected bolus through normal kidneys, corresponding to the renal fraction of cardiac output. After an interval corresponding to renal transit time, this activity exits the kidney, contributing to the down-slope of the washout curve. In the case of  $MAG_3$  with its lower plasma clearance, only half as much will be

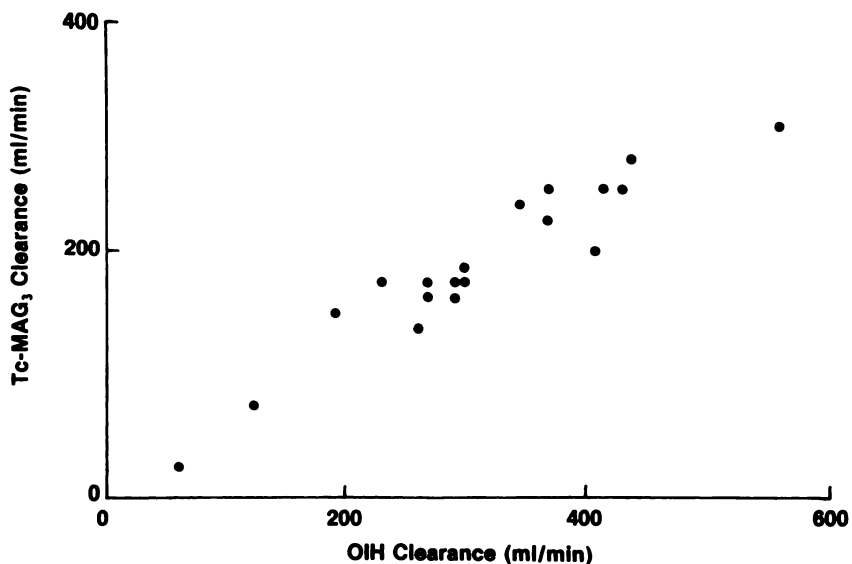


**FIGURE 2**  
Concurrent images for  $[^{99m}Tc]MAG_3$  (left side) and  $[^{131}I]OIH$  (right side), using high energy collimator and  $64 \times 64$  pixel acquisition. A: Normal transplant (routine follow-up). B: Normal (donor evaluation).

**FIGURE 3**  
Slope of renogram washout phase, defined as [peak count rate/(count rate at 20 min)] for [ $^{99m}\text{Tc}$ ]MAG<sub>3</sub> and [ $^{131}\text{I}$ ]OIH. ( $\Delta$ ) Diuretic studies. ( $\bullet$ ) All other studies.



**FIGURE 4**  
Plasma clearance of [ $^{99m}\text{Tc}$ ]MAG<sub>3</sub> versus that of [ $^{131}\text{I}$ ]OIH.

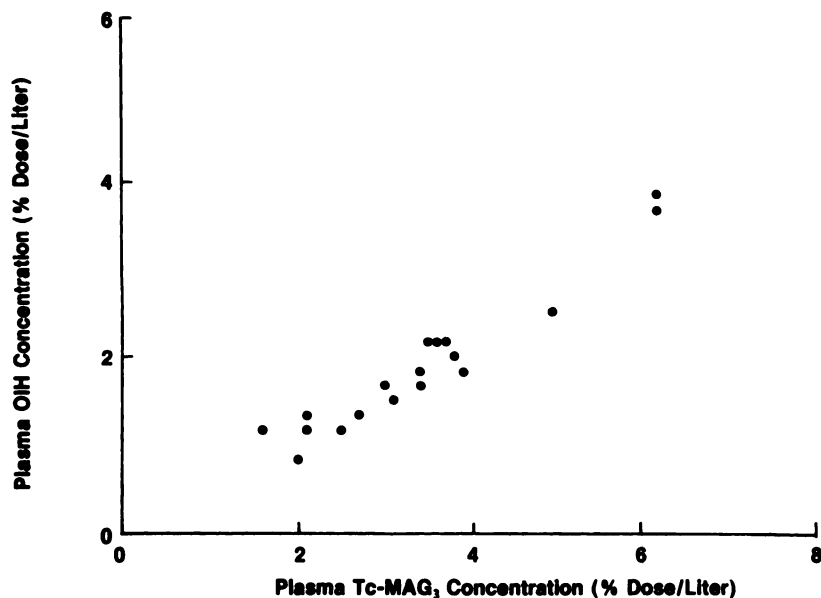


deposited on the first pass, so that the fractional contribution to the peak will be less. The exit of the bolus will be less prominent, resulting in a shallower washout curve.

It is desirable that a replacement for OIH be usable for quantitative measurement of renal function. Our preference is for plasma clearance measurements, which are more accurate, though simpler methods can give clinically useful results. The strong correlation between MAG<sub>3</sub> clearance and OIH clearance (correlation coefficient = 0.96, Fig. 4) suggests that MAG<sub>3</sub> clearance will indeed be a useful measure of renal function. There is substantial red cell penetration by OIH so that early workers with OIH were compelled to show that no shifts between plasma and red cells occurred during sample storage (4). That problem does not exist with MAG<sub>3</sub>, since, as shown above, there is no penetration

of human red cells [though penetration of rat red cells by [ $^{99m}\text{Tc}$ ]MAG<sub>3</sub> has been reported (5)]. The impurity problems that have plagued plasma clearance methods for OIH and for [ $^{99m}\text{Tc}$ ]DTPA have not so far appeared with MAG<sub>3</sub>. We were unable to find impurities, but Dr. Andrew Taylor, using a more sensitive technique, has shown us evidence of several low-level impurities. There is no definite curvature in Figure 4 to suggest the presence of a circulating, poorly excreted impurity, but patients with very high ERPF, for whom the effect would be most pronounced, were lacking in our study population.

Figure 5 suggests a simple method for ERPF estimation using MAG<sub>3</sub>. Our routine method for ERPF estimation is based on the OIH concentration in a single 44-min plasma sample (6). It can be seen from Figure 5 that the 44-min OIH concentration is simply 0.57



**FIGURE 5**  
Plasma concentration at 44 min after injection of [<sup>99m</sup>Tc]MAG<sub>3</sub> versus that for [<sup>131</sup>I]OIH.

times the MAG<sub>3</sub> concentration, so that, by incorporating that factor, our routine formula could be used. However, an optimized technique will require more data.

## CONCLUSIONS

Penetration of red cells by MAG<sub>3</sub> is negligible. In blood, the agent is confined to the plasma, unlike orthoiodohippurate. Clearance from the plasma (ml/min) is about half that of OIH in both normal and diseased kidneys. The correlation is close enough to permit estimation of OIH clearance (hence ERPF) from MAG<sub>3</sub> clearance. To determine the accuracy of this estimation will require the study of a larger group of patients. Plasma concentrations (in % dose/l) are about twice that of OIH, presumably because of greater protein binding. The net effect of higher plasma concentration and lower plasma clearance was an excretion of MAG<sub>3</sub> quite similar to that of OIH. The fraction of the dose found in the urine at 30 min is nearly the same for the two agents and the renogram curves are qualitatively similar. In these 20 cases, which included three with diuretics and two with ACE inhibitors, the differences were too small to influence interpretation.

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