Quantitation of Renal Function with Technetium-99m MAG_3

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

Division of Nuclear Medicine, University of Alabama Hospital, University of Alabama in Birmingham, Birmingham, Alabama; and Nuclear Medicine Service, Birmingham Veterans Administration Medical Center, Birmingham, Alabama

The technetium-labeled hippuran analog [^{99m}Tc]MAG_3 was compared with [^{131}I]hippuran in 50 patients using a quantitative renal function protocol that includes: (a) estimation of effective renal plasma flow by a single-injection, single-sample plasma clearance method, (b) determination of relative function of right and left kidney from the initial count rate over each kidney, and (c) comparison of recovered urine activity with plasma disappearance. This protocol is suitable for routine clinical use, and, in fact, has been used heavily at our clinic for a number of years. By slight modification of the formulas, the results obtained with [^{99m}Tc]MAG_3 agreed well with those using [^{131}I]hippuran. We conclude that [^{99m}Tc]MAG_3 can be substituted for [^{131}I]hippuran in the quantitative protocol, with the better image quality and lower radiation dose (in abnormals) of a technetium-labeled agent.

J Nucl Med 29:1931–1933, 1988

A new technetium labeled physiologic analog of iodine-131 (^{131}I) hippuran, technetium-99m mercaptoacetyltriglycine ([^{99m}Tc]MAG_3), is undergoing clinical trials (*1–5*). Like hippuran, and unlike other renal radiopharmaceuticals, it is avidly secreted by the renal tubules. To determine whether this agent can be used to quantitate renal function, it was compared with hippuran (orthoiodohippurate, [^{131}I]OIH) in 50 patients using a comprehensive renal function protocol that has been described in detail in the literature (*6–13*) and that has been used in our clinic for a number of years (currently, ~ 3,000 studies each year). Under this protocol, renal function is measured as effective renal plasma flow (ERPF) for right and left kidneys separately. An additional parameter is calculated, the "excretory index" (EI), that is used mainly to detect transplant rejection. The [^{131}I]OIH and [^{99m}Tc]MAG_3 were administered simultaneously, using dual-channel techniques both for imaging and for counting plasma and urine.

Received Apr. 11, 1988; revision accepted Aug. 18, 1988.

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

METHODS

The procedure has been described in detail elsewhere (*6–13*). The only differences for this study were: (a) simultaneous administration of 150 or 300 μCi of [^{131}I]OIH and 5 or 10 mCi of [^{99m}Tc]MAG_3 with dual-channel acquisition and counting, and (*6*) use of a slightly longer time interval for determining differential function, 40–140 sec instead of the usual 60–120 sec, to improve the counting statistics slightly. In brief, the protocol consisted of: 1) sequential imaging for 27 min, 2) voiding at 35 min with bladder imaging before and after voiding, 3) imaging the injection site to exclude infiltration, 4) counting the urine, and 5) counting a single 44-min plasma sample. ERPF was calculated from the plasma sample. The fraction of ERPF attributed to each kidney was determined from the background-corrected counts over each kidney for the interval 40 to 140 sec. Urine activity, corrected for postvoid residual from the bladder images, was divided by the activity leaving the plasma to obtain the EI.

The patient population consisted of 50 patients undergoing radionuclide studies of structure and function for routine clinical indications. None had edema or ascites. Twenty-nine of these patients had transplanted kidneys of which 11 were classified as normal, 6 acute tubular necrosis, 11 acute rejection, and one combined acute tubular necrosis with acute rejection. Of the remainder, six patients were found to have no kidney disease, three had cystic disease, three stone disease, three neurogenic bladder, two bladder cancer, two diabetes, one renal artery stenosis, and one chronic renal failure of

undetermined etiology. Forty-nine patients had plasma samples drawn between 42 and 55 min that could be used for ERPF calculation. Twenty-eight patients had urine specimens suitable for calculating EI after excluding those who were unable to void, catheterized, with surgical urinary diversions, or with residual urine activity from a recent [^{131}I]OIH study. In the last event, which occurred in several acutely ill transplant patients, the plasma samples could still be used by subtracting the activity in a pre-injection baseline specimen, but no such correction was possible for the urine. Of the 21 patients that were not transplants, the ^{131}I channel data were lost in one (the first patient of the study) due to operator error, leaving 20 for calculation of differential function.

RESULTS

ERPF was calculated from the [^{131}I]OIH activity in a 44-min plasma sample. As reported previously, there is a proportional relationship between the 44-min [^{99m}Tc]MAG_3 concentration and the 44-min [^{131}I]OIH concentration (*5*). The proportionality constant calculated from the first 20 patients was 0.57 (*5*); including the 30 subsequent patients led to a value of 0.563. By using 0.563 times the [^{99m}Tc]MAG_3 activity in place of [^{131}I]OIH activity for the calculation of ERPF, the results shown in Figure 1 were obtained. One sees that this simple correction gave ERPF values from [^{99m}Tc]MAG_3 in good agreement with those from [^{131}I]OIH (correlation coefficient = 0.96).

The fraction of ERPF attributable to each kidney was calculated by assuming that the ERPF ratio for the two kidneys is the same as the ratio of total background-corrected counts for each kidney over the time interval from 40 to 140 sec after injection. This was calculated separately from the ^{99m}Tc channel and the ^{131}I channel, and the results are shown in Figure 2. Agreement was good (correlation coefficient = 0.99).

The EI is the ratio of activity that appears in the urine to that disappearing from the blood, so that the normal value is 1. Low values indicate retained activity, either in renal parenchyma or collecting system, while high values usually reflect laboratory error. This parameter is useful mainly as a measure of parenchymal retention in transplanted kidneys with either acute rejection or acute tubular necrosis. It is a sensitive indicator of acute rejection (*6,13*). When the urine activity (corrected for bladder residual) was compared for [^{99m}Tc]MAG_3 and [^{131}I]OIH, we found a linear relation that passed almost, but not quite, through the origin. The regression equation was:

$$I = 0.896\ Tc + 0.081.$$

We therefore calculated the EI from the [^{99m}Tc]MAG_3 urine activity, first using the above equation to estimate the corresponding [^{131}I]OIH urine activity, and then using the usual formulas (*12*). (In addition to the urine activity, the calculation of EI requires an estimate of ERPF, which was obtained from the 44-min [^{99m}Tc]MAG_3 plasma concentration, as described above.) The results are shown in Figure 3. Again there was good agreement (correlation coefficient = 0.96).

DISCUSSION

Technetium-99m MAG_3 has higher protein binding, higher plasma concentration, and lower plasma clearance than [^{131}I]OIH (*2–5*). Calculation of ERPF and EI from [^{99m}Tc]MAG_3 thus required modification of the methods used for [^{131}I]OIH. The agreement between

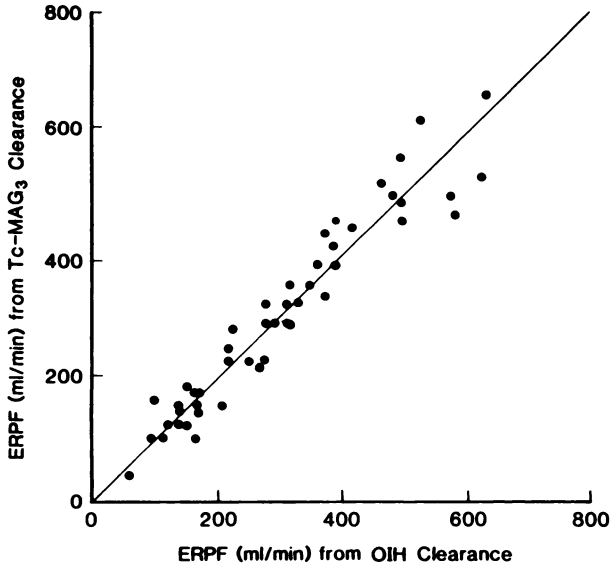

FIGURE 1
Effective renal plasma flow calculated from [^{99m}Tc]MAG_3 versus that calculated from [^{131}I]hippuran. The line of identity is shown.

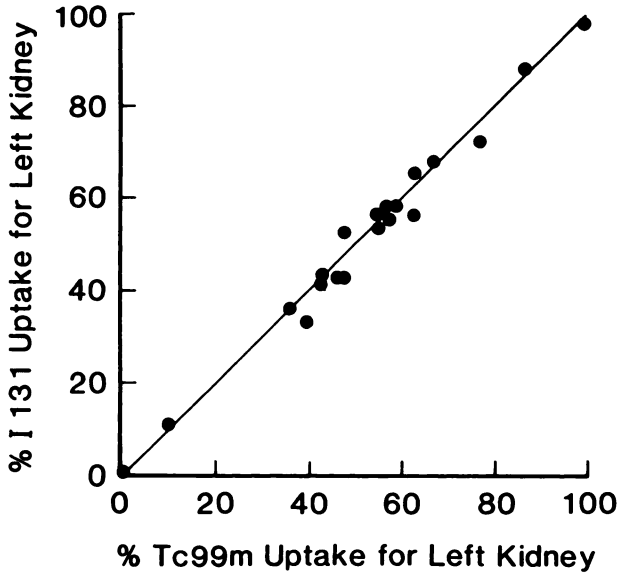

FIGURE 2
Uptake by left kidney, as % of total for both kidneys, for [^{99m}Tc]MAG_3 versus that for [^{131}I]hippuran (at 40–140 sec, with background subtracted). The line of identity is shown.

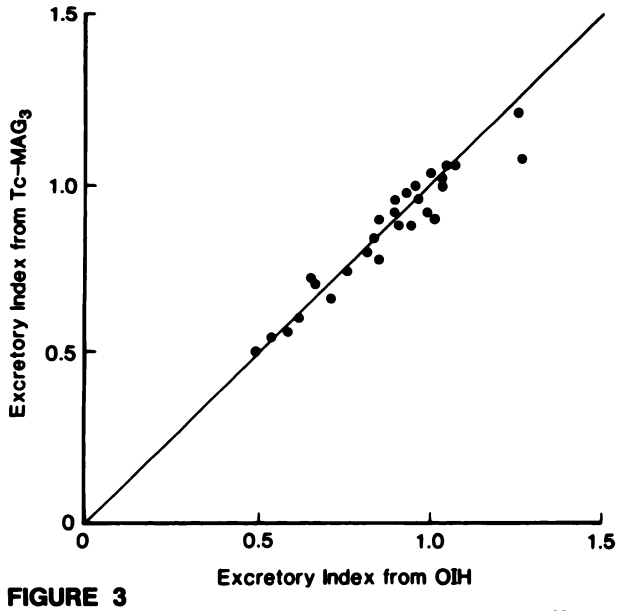

FIGURE 3
Excretory index (defined in text) calculated from [^{99m}Tc]MAG_3 versus that calculated from [^{131}I]hippuran. The line of identity is shown.

[^{131}I]OIH and [^{99m}Tc]MAG_3 shown in Figure 1, while good, was not as good as the agreement between [^{123}I]OIH and [^{131}I]OIH found in a previous study using the same protocol (*14*), further illustrating that the agents are similar but not identical.

The above methods for estimating ERPF and EI from [^{99m}Tc]MAG_3 are not necessarily the best, and alternative approaches are being explored. Bubeck et al. suggest using MAG_3 clearance itself as a measure of renal function, without converting to ERPF (*3*). This is a reasonable approach and single-sample methods could be developed. It has been reported that urinary protein loss affects [^{99m}Tc]MAG_3 clearance (*15*), but supporting data have not yet appeared; further study is needed. Edema and ascites are apt to cause problems, though perhaps less with [^{99m}Tc]MAG_3 than with other agents because of its intravascular retention. With our protocol, none of the 50 cases studied showed clinically significant differences between the two agents when the appropriate corrections were made, so it is clear that useful quantitation is possible in most cases. The methods presented here appear adequate for clinical use and can be used with existing software on several commercially available nuclear medicine computing systems.

CONCLUSION

With certain simple corrections, [^{99m}Tc]MAG_3 could be substituted for [^{131}I]OIH in a quantitative renal function protocol that is used routinely in our clinic and that has previously been described in detail. No clinically significant differences were found in 50 patients.

ACKNOWLEDGMENTS

The authors thank Ms. Dorothea Ballard for assistance with the manuscript. This work was supported by Mallinckrodt, Inc., and by the Birmingham Veterans Administration Medical Center.

REFERENCES

1. Fritzberg AR, Kasina S, Eshima D, Johnson DL. Synthesis and biologic evaluation of technetium-99m MAG_3 as a hippuran replacement. *J Nucl Med* 1986; 27:111–116.
2. Taylor A, Eshima D, Fritzberg AR, Christian PE, Kasina S. Comparison of I-131-OIH and technetium-99m-MAG_3 renal imaging in volunteers. *J Nucl Med* 1986; 27:795–803.
3. Bubeck B, Brandau W, Steinbaecher M, et al. Technetium-99m labeled renal functioning and imaging agents: II. Clinical evaluation of ^{99m}Tc-MAG_3 (^{99m}Tc-mercapto-acetylglycylglycylglycine). *Nucl Med Biol* 1988; 15:109–118.
4. Jafri AR, Britton KE, Nimmon CE, et al. Technetium-99m-MAG_3, a comparison with iodine-123 and iodine-131-orthoiodohippurate in patients with renal disorders. *J Nucl Med* 1988; 29:147–158.
5. Russell CD, Thorstad B, Yester MV, et al. Comparison of Tc-99m-MAG_3 with I-131-hippuran by a simultaneous dual channel technique. *J Nucl Med* 1988; 29:1189–1193.
6. Dubovsky EV, Logic JR, Diethelm AG, et al. Comprehensive evaluation of renal function in the transplanted kidney. *J Nucl Med* 1975; 12:1115–1120.
7. Kontzen FN, Tobin M, Dubovsky EV, Tauxe W. Comprehensive renal function studies: technical aspects. *J Nucl Med Technol* 1977; 5:81–84.
8. Tauxe WN, Tobin M, Dubovsky EV, Bueschen A, Kontzen F. A macrofunction for computer processing of comprehensive renal function studies. *Eur J Nucl Med* 1980; 5:103–108.
9. Tauxe WN, Dubovsky EV, Kidd T, Diaz C, Smith LR. New formulas for the calculation of effective renal plasma flow. *Eur J Nucl Med* 1982; 7:51–54.
10. Tauxe WN, Dubovsky EV, Kidd T, Smith LR, Lewis R, Rivera R. Prediction of urinary excretion of ^{131}I-orthoiodohippurate. *Eur J Nucl Med* 1982; 7:102–103.
11. Dubovsky EV, Russell CD. Quantitation of renal function with glomerular and tubular agents. *Semin Nucl Med* 1982; 2:308–329.
12. Dubovsky EV. Comprehensive renal function studies with iodine-131-OIH. In: Tauxe WN, Dubovsky EV, eds. *Nuclear medicine in clinical urology and nephrology.* Norwalk, Conn: Appleton-Century-Crofts; 1985:157–170.
13. Dubovsky EV. Renal Transplantation. In: Tauxe WN, Dubovsky EV, eds. *Nuclear medicine in clinical urology and nephrology.* Norwalk, Conn: Appleton-Century-Crofts; 1985:233–278.
14. Russell CD, Dubovsky EV. Uncontrolled variables in the measurement of renal function (Letter). *J Nucl Med* 1986; 27:1644.
15. Schaap GH, deJong RBJ, Alferink THR, Roos JC, Donker AJM. ^{99m}Tc-MAG_3 is not suitable for determination of the effective renal plasma flow [Abstract]. *Kidney Int* 1987; 32:775.