Technical Procedures for Use of the New Kidney Agent Technetium-99m MAG3™

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This is the third article in a four-part series on new radiopharmaceuticals. Upon completion of this article, the technologist should be able to (1) identify the benefits of imaging with MAG3, (2) recognize the different properties of the imaging agents DTPA, OIH, and MAG3, (3) utilize developed imaging techniques, and (4) identify some abnormal conditions.

With the release of technetium-99m MAG3 for routine clinical use in 1990 in the United States (earlier abroad), an agent has become available that combines the rapid kidney uptake of orthoiodohippurate (OIH) with the desirable imaging properties of ^{99m}Tc. Those familiar with the uses of the earlier agents ^{99m}Tc-DTPA and iodine-131 (^{131}I) or iodine-123 (^{123}I) OIH will have little to learn that is new; flow studies ("radionuclide angiograms") with MAG3 will be fairly similar to those with DTPA, and renograms will be quite similar to those with OIH. However, the count rate is some fifty times higher than with OIH, more than some older software can handle.

MAG3™ (Mallinkrodt Medical, Inc., St. Louis, MO) was introduced by Fritzberg and others in 1986 as a "designer drug" having a molecular structure that was chosen to eliminate certain stereochemical problems that arose with earlier agents. It was shown by Taylor and others to function in humans as a technetium-labeled physiologic analog of OIH (*1, 2*). Although developed at the University of Utah, subsequent clinical testing was conducted abroad, and approval for routine use was granted in several European countries well before MAG3 was available in the United States.

MAG3 is excreted primarily by tubular secretion, like OIH. As George Taplin, who introduced OIH, pointed out for that agent, this does not mean that renal uptake is a measure of tubular function. Uptake is better thought of as a measure of renal blood flow. For OIH, most of the agent that enters the kidney through the renal artery is extracted from the blood and excreted into the tubular lumen, remaining in the renal parenchyma for a few minutes as it flows down the tubule, and finally passing through the collecting system and ureter to the bladder. The activity in the kidney during the first few minutes is thus directly proportional to renal blood flow.

In the case of MAG3, only about half of the activity that enters the kidney is extracted from the blood on its way through the kidney. However, less of the dose diffuses out of the blood vessels into other tissues, being partly bound by plasma protein, so that the blood concentration is thus about twice as high as for OIH. The high concentration makes up for the low extraction so that the kidney and bladder time-activity curves for MAG3 are almost identical to those for OIH, and the fraction of administered dose in kidney or bladder at a given time is almost the same for the two agents. In other words, the renogram curves will be essentially the same for MAG3 as for OIH, so that the well-developed techniques for OIH can be used for the new agent MAG3 (*2–6*).

The flow study or radionuclide angiogram for MAG3 will differ somewhat from that for DTPA since a greater percentage (50%–65%) of the activity entering the kidney will remain there. For DTPA, only 20% of the activity remains in the kidney and the initial bolus can be seen to enter and leave the kidney. With MAG3, so much remains in the kidney that the exit of the bolus may not be detectable from inspection of the time-activity curve.

Kidney function can be measured from the plasma clearance of MAG3 or, less accurately, from kidney or bladder uptake measured with the gamma camera. MAG3 clearance has been found to be proportional to OIH clearance, and can thus be used as a measure of effective renal plasma flow (ERPF) (*4, 7, 8*). The ERPF has been heavily used as a clinical measure of renal function at our clinic for over ten years. It can be used in much the same way as the more commonly used glomerular filtration rate (GFR). In most chronic disorders, ERPF is about five times the GFR. Since MAG3 is

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cleared much faster than DTPA, its plasma clearance can be measured accurately in less than an hour, unlike DTPA, which requires at least two hours and preferably three for measurements of comparable accuracy.

One of the joys of nuclear medicine is that no two centers do anything the same way. This helps to maintain the distinction between a technologist and a technician. In the remainder of this manuscript we shall describe how things are done at this point in time at our two hospitals, the University of Alabama at Birmingham and the Alabama Children's Hospital. The careful reader will notice differences even between these two institutions, which are only three blocks apart and affiliated with the same medical school. We shall try to indicate areas of controversy, but it is beyond the scope of this paper to justify every decision. In some cases the only justification is that we tried it and it seems to work.

Some typical studies are shown in Figures 1–3. Figure 1 is an example of a normal MAG3 study. It was done at the same time as a [^{131}I]OIH study using a dual-channel technique, and the renogram curves are shown for both studies to demonstrate their similarity. Figure 2 is an example of a patient with renal artery stenosis studied with an ACE inhibitor. Note the decreased uptake by the left kidney in the first frame, indicating decreased blood flow and the delayed clearing of activity from the parenchyma on the delayed images. The latter finding is more specific for renal artery stenosis, and can be seen even in the absence of asymmetric initial uptake. Figure 3 is an example of diuretic renography. There is abnormal retention of activity in the collecting system that nevertheless clears on diuretic administration, indicating lack of significant obstruction.

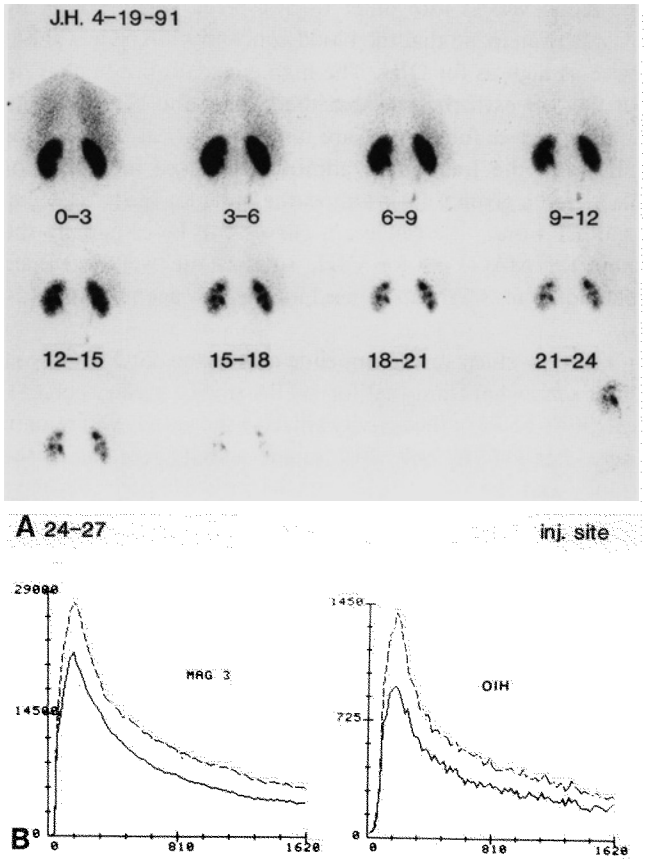

FIG. 1. Normal kidneys. (A) MAG3 images. (B) Renal time-activity curves for both MAG3 and simultaneously administered [^{131}I]OIH.

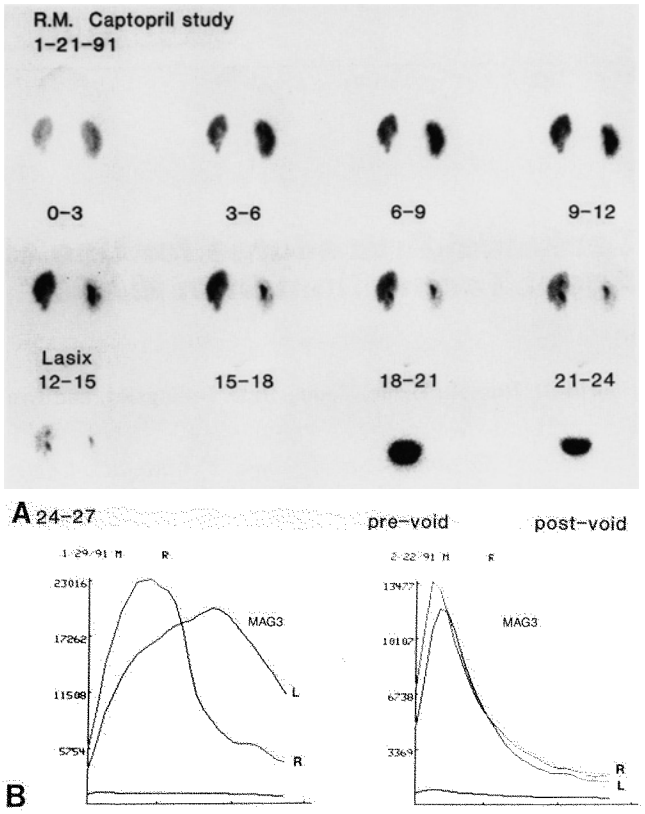

FIG. 2. Left renal artery stenosis, captopril study. (A) MAG3 images prior to angioplasty. (B) MAG3 time-activity curves before angioplasty (curves on left) and afterward (curves on right).

RADIOPHARMACEUTICAL PREPARATION AND DOSIMETRY

Preparation entails 10 min in a boiling water bath for labeling, and rapid chromatography on a disposable Waters Sep-Pak® (Millipore Corporation, Milford, MA) for quality control. The product will initially contain from 2 to 25 mCi/ml of ^{99m}Tc and can be used for 6 hr after preparation. For details, follow the package insert.

The target organ is the bladder wall, with an estimated dose of 0.48 rad/mCi (0.13 mGy/MBq) for the adult. Estimated total body dose is 0.0067 rad/mCi (0.0018 mGy/MBq). Doses for other organs are cited in the package insert. With normal renal function, most of the dose will be in the bladder one-half hour after injection. If the patient voids at that time, unnecessary additional exposure can be prevented. This should be routine in pediatric patients.

RENAL IMAGING WITH MAG3

Low urine flow rates can mimic obstruction and can prevent collection of an adequate urine sample for determination of the excretory index (EI). When practical, 500 cc water are

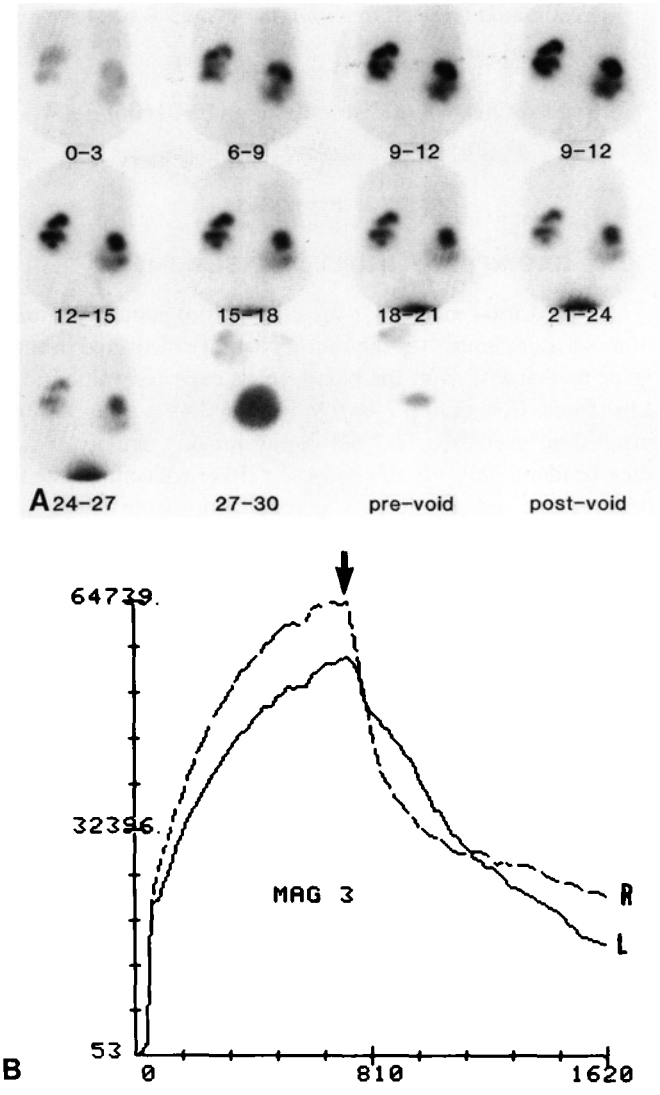

FIG. 3. Bilateral medullary sponge kidney, diuretic study. (A) MAG3 images. (B) Time-activity curves with arrow indicating time of furosemide administration.

given 30 min prior to the examination, but we are not adamant and many of our patients are at ambient hydration, or even dehydrated in order to perform an excretory urogram on the same visit. Since diuretics are used whenever there is a clinical question of obstruction, this approach rarely causes problems.

Unless a urine specimen must be obtained for counting (e.g., to calculate EI), the patient should void just before the study is begun to avoid the need to urinate during imaging.

Posterior supine views are obtained with the following exceptions. In patients with renal transplants, the views are acquired in the anterior supine position, while views of patients with urinary diversions (ileal loops) are acquired in the posterior sitting position to facilitate drainage. The heart should be included in the field of view (except for transplants) if deconvolution analysis is planned; otherwise the bladder should be included.

The camera is started simultaneously with injection and the first 60 sec are acquired as 1-sec, 64 × 64-pixel frames. The next 26 min are acquired as 20 sec frames. To permit ERPF and EI measurement, these are followed by a one-min image of the injection site and one-min images of the bladder immediately before and after voiding. (Voiding should occur at 35 min after injection.) This acquisition protocol will suffice for most published processing techniques, but if ureteral peristalsis is to be analyzed, a minimum of several minutes of 1-sec to 2.5-sec frames must be acquired after activity reaches the ureter.

A complete ring around each kidney is used as the background region-of-interest for that kidney. One-min intervals are used for the time-activity curves without smoothing or decay correction.

Differential function is calculated as the fraction of total background-corrected counts over each kidney from 60 sec to 120 sec after injection.

To calculate residual urine volume and EI, background-corrected bladder counts are obtained from the pre- and post-void bladder images. A background region-of-interest lateral to the bladder is used, and no decay correction is required.

The images are displayed as a radionuclide angiogram of fifteen 4-sec frames, a "renogram" sequence of nine 3-min frames (reframed to include the 60 one-sec frames as part of the first 3-min frame), and static images of the injection site and of pre-void and post-void bladder. Background-corrected time-activity curves are displayed for each kidney.

ERPF MEASUREMENT WITH MAG3

The ERPF is a measure of renal function and can be used, like GFR or creatinine clearance, to evaluate function and monitor changes. In most chronic renal diseases, the filtration fraction is largely unaffected so the GFR can be estimated by dividing the ERPF by 5. In acute renal failure or transplant rejection, the GFR typically decreases more than the ERPF (filtration fraction decreases). This situation is identified on the MAG3 study by noting prolonged parenchymal transit on the images.

The single-sample method may be unreliable in the presence of significant edema or ascites, so these conditions should at least be noted. When the ERPF value is below around 125 ml/min, the percentage error in the measurement may be large, but it should still correctly indicate that the function is low.

No patient preparation is required for ERPF alone, although there may be requirements for any concurrent imaging studies. While ERPF is subject to diurnal variation and other physiologic and pharmacologic influences, we have found no effect large enough to cause serious problems in using ERPF as a clinical measure of renal function. For research use, however, the time and conditions of measurement should be as uniform as is practical.

Identical volumes corresponding to about 5 mCi are drawn into multiple syringes for individual doses and a standard. This is our preferred dose for combined imaging and ERPF measurement. For ERPF measurement only, as little as 0.1 mCi should suffice while useful images can be obtained with

2 mCi or even less. For optimum radionuclide angiograms, 10 mCi should be used, calibrated for the time of injection. The syringe size should be chosen so that it is at least ⅓ filled to facilitate measurement. Verify in a dose calibrator that each patient dose agrees with the standard to within 5%.

The standard dose from the syringe is injected into a 100 ml volumetric flask nearly full of tap or distilled water, rinsing the syringe three times with water from the flask. It is mixed well, brought to the volume mark, and mixed again. One ml is transferred to another 100 ml volumetric flask, brought to the mark, and mixed well. This effectively dilutes the standard to a volume of 10 liters, so that its activity will be comparable to that in the plasma.

After injection the syringe is rinsed twice with blood. One may check for residual syringe activity, but we have found it negligible after the blood rinses. The injection site must be examined for infiltration of the dose, preferably by imaging, or alternatively with a partly shielded survey meter, at 30–45 min after injection.

A blood sample is obtained in an EDTA tube at 45 min after injection, using the arm opposite the injection site when possible. The time can range from 40 to 55 min, but greatest accuracy is obtained at 45 min. Both injection and sampling can be performed if necessary through the same indwelling catheter, but the catheter should be thoroughly flushed with saline after injection and with blood before sampling. The plasma is centrifuged and separated on the day of the study, since it is not certain how long the agent is stable in plasma. Once separated, its chemical form no longer matters, so it can be counted the next day. Laboratory worksheets should record the time of injection, time of sampling, and time of counting.

When counting specimens on the day of injection, 0.1 ml of plasma and standard are used to avoid overloading the counter. Older counting equipment should be checked to see if it can accommodate these count rates. One verification method is to recount the next day and see if the results change. Duplicates of plasma and standard are counted and the results averaged. When counting the day after injection, 1 ml can be used but volumes of plasma and standard should be identical to keep counting geometry constant. Each plasma sample should be counted within a few minutes of the standard to make the decay correction negligible. Multiple standards can be pipetted from the stock solution if needed.

The plasma counts are multiplied by 0.563 (to correct for the difference between MAG3 and OIH) and then used in the Tauxe formulas (*7*, *9*). While the Tauxe formulas can be calculated by hand, they are easily programmed, which makes the results less prone to error. A number of commercial computer software systems contain them already. Newer software should offer a MAG3 option with appropriate correction factors built in, but it must be applied manually to the plasma counts when using older software.

Following is a sample calculation using the Tauxe formulas (*9*) for OIH (see Figure 1 of that paper). Plasma is 6224 counts/0.1 ml, standard is 31606 counts/0.1 ml, and the sample time is 49 min after injection.

$$\text{estimated OIH plasma counts} = 0.563 * 6224 = 3504$$

$$\text{estimated OIH vol of distribution} = (10*31606)/3504 = 90.0 \text{ liters}$$

$$\text{ERPF} = 492 \text{ ml/min}$$

EXCRETORY INDEX MEASUREMENT

The EI is used mainly for the diagnosis of acute rejection in renal transplants. It is the ratio of activity recovered in the urine to that lost from the blood, so its expected value is 1. Low values (less than 0.7 or 0.8) indicate less activity in the urine than expected. The site of the missing activity must then be identified from the images in either collecting system (obstruction, dehydration) or parenchyma (acute rejection, acute tubular necrosis). High values, above 1.2, usually signal laboratory error. If the post-void residual is large, the EI is less accurate, since the correction for residual urine is imperfect. The EI is an adjunct to an imaging study, and requires both imaging and ERPF measurement.

Immediately before and after voiding, the bladder is imaged, and background-corrected bladder counts obtained to estimate the post-void residual urine in the bladder. The patient is asked to void as completely as possible at 35 min after injection, with collection of the entire specimen. The volume of the specimen is measured using a graduated cylinder. The urine volume, time of injection, time of voiding, time of counting, and time of bladder imaging are recorded on the laboratory worksheet.

One ml of urine is diluted to 100 ml using volumetric glassware and quantitative technique. One tenth ml of the diluted urine is counted with identical volumes of standard and plasma. If counting is postponed, a larger volume may be used, but the volume of the standard must always match the volume of the sample to keep counting geometry consistent, and the sample must be counted within a few minutes of the standard to avoid the need for decay corrections. Counts in the total specimen are calculated using the specimen volume and the dilution factor.

The post-void residual urine counts are estimated by proportion from the background-corrected pre- and post-void bladder counts and the urine specimen counts. The counts in the residual urine are added to the counts in the specimen to obtain the total urine counts. The total urine counts can then be expressed as a fraction of the administered dose and converted to the corresponding value for OIH using a published formula (*7*). Subsequent calculations proceed exactly as for OIH (*10*, *11*). These calculations are best done by computer, though hand calculation is possible.

A number of commercial computer systems include software for similar studies with OIH. These older systems can be used by entering the total urine counts for MAG3 in place of those for OIH, and then applying the correction as follows:

$$\text{EI} = (0.896*\text{total MAG3 excretion} + 8.1)/\text{expected OIH excretion}$$

Since the available formulas for expected excretion give a result for OIH, the total excretion of MAG3 must be converted to the corresponding value for OIH. In the above formula, total and expected excretion are to be expressed as a percent of the administered dose. The correction is small when function is normal.

Following is a sample calculation where urine is 16578 counts, standard is 31606 counts, pre-void is 60200 counts, post-void is 1449 counts, urine volume is 130 ml, ERPF is 492 ml/min, and expected OIH excretion is 71.8% (obtained by applying Tauxe formulas [*11*]).

$$\text{actual void} = (16578*130)/31606$$
$$= 68.2\% \text{ of dose}$$
$$\text{total excretion} = (68.2*60200)/(60200-1449)$$
$$= 69.8\%$$
$$\text{EI} = (0.896*69.8 + 8.1)/71.8$$
$$= 0.983$$

DIURETIC RENOGRAPHY WITH MAG3

This procedure is used to diagnose urinary tract obstruction. The use of diuretics as an adjunct to renography separates patients with obstruction from patients without obstruction who have delayed pelvic clearance due to a dilated collecting system.

Ten min after injection of MAG3, 0.5 mg/kg furosemide is administered intravenously (up to a maximum permissible dose of 40 mg). Failure of pelvic activity to clear with furosemide in a normally functioning kidney or one with unilateral ERPF > 100 ml/min indicates obstruction. The test is only reliable when the underlying renal function is good enough, hence the condition on ERPF. In borderline cases, the ratio of background-corrected counts at peak activity to that at 27 minutes can be used as a criterion of response; values less than 1.5 in a kidney with normal parenchymal function indicate obstruction.

The timing of the diuretic dose varies from center to center. Equivocal responses have been reportedly resolved in some cases by repeating the study with the furosemide given 15 min prior to administration of the radionuclide. Some centers increase the furosemide dose if renal function is known to be poor. A variety of methods can be used to quantitate pelvic washout, such as half-time after peak. The above is one of the simplest.

ACE-INHIBITOR RENOGRAPHY WITH MAG3

This test is used to diagnose renal artery stenosis or to assess the functional significance of a previously identified anatomic stenosis. The study often becomes more abnormal or converts from normal to abnormal when ACE inhibitors are given.

The patient should not eat for 4 hr prior to the procedure to ensure prompt absorption of the oral captopril, but fluids should not be withheld. For patients having a baseline study after a positive ACE-inhibitor study, all ACE inhibitors must be discontinued for 48 hr in advance, except that 24 hr suffices after a single dose of captopril.

Our practice is to perform the initial study with ACE inhibitor. If the initial study is abnormal, a repeat study without captopril may be performed to determine whether the abnormality is captopril-induced. Sometimes when the initial study is abnormal, the patient proceeds directly to arteriography.

One hour prior to the study an oral dose of 25 mg captopril is given. The blood pressure must be monitored before and after the dose and emergency medical assistance must be available. Routinely the blood pressure is recorded before captopril administration and every 15 min for 1 hr, at which time imaging begins. To ensure blockade, we administer the captopril dose even when the patient is already taking ACE inhibitors. Severe hypotensive reactions can occur that require immediate treatment by infusion of normal saline and possibly other supportive measures. Patients that are salt depleted, e.g., by diuretics, are at increased risk.

A florid response consists of rapid uptake of tracer by the affected kidney, with all the activity remaining in the parenchyma and none appearing in the collecting system for the duration of the study. Less dramatic responses are also seen, characterized by delayed transit of activity through the kidney, delayed peak time, and transient retention in the collecting system. Techniques and diagnostic criteria are still evolving, but there appears to be consensus that a florid captopril-induced unilateral response is quite specific for functionally significant renovascular disease. Bilateral response, even when florid, is less reliable.

Note that the florid response seen with MAG3 or OIH, intense activity in the affected kidney on delayed images, is almost the opposite of that seen with DTPA. When DTPA is used, the affected kidney shows diminished uptake or none at all.

Current controversial issues include the optimum dose of captopril, whether to use captopril or enalopril, how long ACE inhibitors need be stopped before a baseline study, and the criteria for interpretation. Other areas that have not been adequately addressed are the effects of fluid load and salt intake.

RENAL IMAGING WITH MAG3 IN CHILDREN

The study is performed with indwelling bladder catheter and after intravenous hydration with 5% dextrose in 0.25 N saline, 10–15 ml/kg over 30 min, ending immediately prior to injection. The bladder is catheterized with an 8 French 42″ feeding tube, using sterile technique. The dose ranges from 0.5 to 6 mCi and is based on the age of the patient as outlined in Table 1.

One-min 128 × 128 pixel frames are acquired for 30 to 60 min (to include at least 20 min after furosemide administration), using a high resolution collimator. The patient is imaged posteriorly in the supine position; immobilized but without sedation.

TABLE 1. MAG3 Dose Ranges in Children

Age (yr)	Prescribed dose (mCi)
0–1	0.5–1.0
1–3	1.0–1.5
3–5	1.5–2.0
5–7	2.0–2.5
7–9	2.5–3.5
9–11	3.5–4.5
11–13	4.5–5.5
13–15	5.5–6.0
15–adult	6.0

When ACE inhibitors are used, bladder catheterization and intravenous access are still used, but a pediatric nephrologist is consulted for the hydration procedure and dose of captopril. Typically 50 mg of oral captopril are used 30 min prior to the start of the renogram. The venous access is installed as a precaution even when additional hydration is not desired.

Intravenous furosemide (1 mg/kg up to 40 mg maximum) is given at peak pelvic filling. For repeat studies, the same injection time is used. Regions of interest are designated for each kidney (including pelvis) and a single semilunar background region is selected inferior to one kidney.

A dynamic sequence of 1-min images is shown together with background-corrected time-activity curves. No correction is used for radioactive decay. Relative counts (in percent) are shown for each kidney for the second minute after injection, and the washout half-time from peak activity is calculated.

Interpretation is based primarily on subjective evaluation of the images, with particular attention to the clearance of activity from the collecting system after furosemide administration.

The standard procedure is a diuretic renogram because most pediatric referrals involve a question of obstruction. We use this procedure for all pediatric renal studies even though a simpler approach might be appropriate in selected cases.

CONCLUSION

We have described our technical procedures for renal imaging with ^{99m}Tc-MAG3. These are given in detail as currently performed at the University of Alabama in Birmingham and at the Alabama Children's Hospital. Areas of controversy are indicated, but arbitrary choices have been made in the selection of methods.

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