Technetium-99m-MAG3 in Early Identification of Pyelonephritis in Children

Reinaldo Laguna, Frieda Silva, Elba Orduña, James J. Conway, Sue Weiss and Cindy Calderon
Nuclear Medicine Section, Department of Radiological Sciences, University of Puerto Rico School of Medicine, San Juan, Puerto Rico; and Children's Memorial Hospital, Chicago, Illinois

The purpose of this study was to determine whether ^{99m}Tc-mercaptotriacetylglycine (MAG3) can substitute for ^{99m}Tc-glucoheptonate (GH) in the detection of pyelonephritis. **Methods:** One hundred thirty renal scintigraphies were evaluated retrospectively in 38 children (21% boys, 79% girls; age range 1 mo–21 yr; mean age 7.2 yr) referred for evaluation during an acute clinical urinary tract infection and for follow-up studies. Twelve topographical regions were designated on each kidney. Each area was graded for severity of decreased radionuclide localization: mild (Grade 1), moderate (Grade 2) or marked (Grade 3). Early posterior views of MAG3 studies were compared to delayed posterior GH images. In all patients, both studies were performed on the same day. **Results:** Eighty-two studies were performed during an acute clinical infection and 48 were performed as follow-up. Seventy-seven percent of the studies had focal cortical lesions. Of all the cortical lesions identified by GH, MAG3 detected 74% (match lesions). A comparable percentage of lesions was identified in each region by both studies. GH scintigraphy detected 261 lesions (63 Grade 1, 149 Grade 2 and 49 Grade 3), and MAG3 detected 201 lesions (37 Grade 1, 117 Grade 2 and 47 Grade 3). MAG3 was unable to recognize 60 lesions identified by GH studies in 11 patients (mismatch lesions). Of these, 41% (26 of 63) were Grade 1, 21% (32 of 149) were Grade 2 and 4% (2 of 49) were Grade 3. In three cases, MAG3 identified lesions not seen by GH (reverse mismatch); all had acute symptomatic infection. **Conclusion:** These data document that MAG3 in the early phase of the study (1–2 min) can detect Grade 2 to Grade 3 cortical lesions in patients with pyelonephritis, but it is less effective in detecting Grade 1 lesions.

Key Words: cortical scintigraphy; pyelonephritis; technetium-99m-scintigraphy; technetium-99m-glucoheptonate; mercaptotriacetylglycine

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Pyelonephritis is a frequent infectious process in the pediatric population that results in acute and chronic complications. The clinical presentation and laboratory findings comprise a spectrum of signs and symptoms that are a challenge to the clinician (*1–5*). The histologic findings follow a temporal relation: interstitial nephritis, vasculitis and frank pus (*5*). Lesions in pyelonephritis have been described as solitary focal, multifocal or diffuse, involving the entire kidney (*6*). Multiple different imaging modalities have been advocated for its evaluation (*7–9*). Cortical scintigraphy has proven to be the most sensitive method in establishing this diagnosis (*1,8,10–12*).

Studies with ^{99m}Tc-dimercaptosuccinic acid (DMSA) or ^{99m}Tc-glucoheptonate (GH) are recognized by many as the gold standard in the detection of parenchymal changes in acute and chronic pyelonephritis (*1,2,11*). Technetium-99m-mercaptotriacetylglycine (MAG3) is the more recently developed radiopharmaceutical for renal studies in nuclear medicine. It rapidly localizes in the renal parenchyma during the early phase of the study (1–2 min). This early image allows the evaluation of the renal cortical parenchyma because the intrarenal distribution of MAG3 may be similar to that of GH. The abnormalities identified should be comparable to those seen on delayed GH or DMSA images.

The aim of this study was to compare the ability of MAG3 early scintigraphy with GH delayed posterior images to detect cortical lesions in pyelonephritis. We evaluated the utility of high-resolution MAG3 images for the detection of cortical abnormalities at different stages of pyelonephritis and determined whether MAG3 can substitute for GH in the detection of pyelonephritis.

MATERIALS AND METHODS

We performed a retrospective analysis of the renal studies performed at the nuclear medicine service of Children's Memorial Hospital (Chicago, IL) during the period 1988–1994. All studies of patients with an acute clinical urinary tract infection who had a follow-up study were evaluated. All patients had MAG3 and GH renal scintigraphies performed on the same day. The MAG3 study was performed first, followed by the GH scintigraphy. The imaging protocols are described in Table 1.

A topographical map, with 12 regions, was designed to specifically localize the lesions in each kidney (Fig. 1). Each region was compared to its equivalent on both scintigraphies. A grading system, based on the amount of decreased radionuclide localization, was used to establish the severity of the inflammatory process (Table 2). All studies were evaluated independently by two experienced nuclear medicine physicians who were blinded to clinical data and study results. The early posterior image of the MAG3 study was compared only to the delayed posterior view of the GH study. Each lesion was localized and graded according to the above parameters.

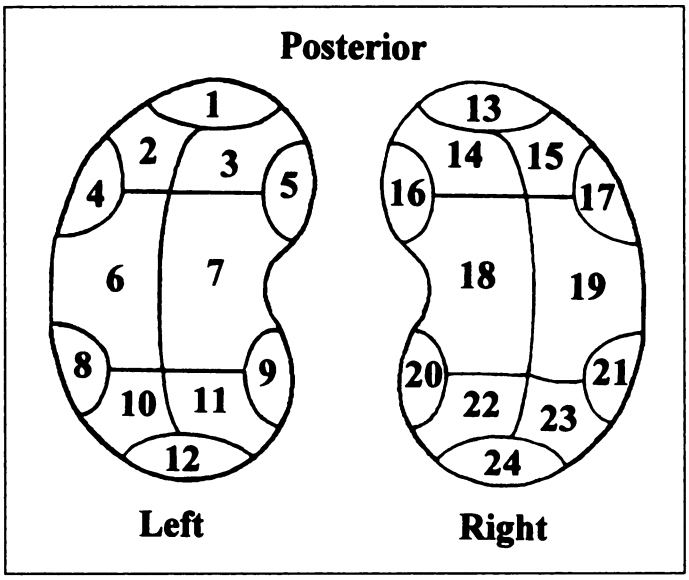

FIGURE 1. Renal topographical map.

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For correspondence or reprints contact: Reinaldo Laguna, MD, Nuclear Medicine Section, Department of Radiological Sciences, University of Puerto Rico School of Medicine, P.O. Box 365067, San Juan, Puerto Rico 00936.

TABLE 1
Acquisition Protocol

	Technetium-99m-MAG3 (50 μCi/kg; minimum 1 mCi)	Technetium-99m-glucoheptonate (100 μCi/kg, minimum 2.5 mCi)
Collimator	High resolution	Converging
Acquisition protocol	Magnification (to improve image quality) varied from xiphoid process to symphysis pubis as per patient size, 2-min renography images for 20 min, diuresis phase proceeded for additional 20 min	Magnification of static images, for 200,000–400,000 counts, 1.5–2.5 hr after injection following the MAG3 images with diuresis

RESULTS

One hundred thirty renal scintigraphies (65 GH, 65 MAG3) were evaluated retrospectively in 38 pediatric patients [8 boys (21%) and 30 girls (79%); age range 1 mo–21 yr; mean age 7.2 yr]. Eighty-two studies were performed during an acute clinical infection. Forty-eight studies were performed at follow-up at different time intervals. Some of these were performed during a new acute infection. Seven patients required more than one follow-up study, as requested by the primary physician. Studies (initial and follow-up) were evaluated independently. Each region of the MAG3 study was compared to its equivalent region on the GH study to differentiate acute pyelonephritis from a cortical scar.

Seventy-seven percent (100 of 130) of the scintigraphies identified at least one focal cortical lesion in the renal topographical map. A total of 270 new lesions were identified in 100 abnormal scintigraphies, 82 of which were performed during an acute clinical pyelonephritis and 18 of which were performed in a recurrent acute infection. There were 64 Grade 1 lesions, 157 Grade 2 lesions and 49 Grade 3 lesions. The GH scintigraphies detected 261 lesions: 63 were Grade 1, 149 were Grade 2 and 49 were Grade 3. Of these, MAG3 studies detected 201 lesions: 37 were Grade 1, 117 were Grade 2 and 47 were Grade 3 (Table 3). There was no significant difference in the number of lesions identified by each study in any particular anatomical region (Fig. 2).

MAG3 scintigraphy was unable to recognize 60 lesions identified in the GH study (Fig. 3). Forty-one percent were Grade 1, 21% were Grade 2 and 4% were Grade 3. In three patients, MAG3 identified 9 lesions not seen by GH: 1 lesion was Grade 1 (2%), and 8 (5%) were Grade 2 (Table 1). All these

TABLE 2
Grading System for Renal Lesions

	Grade	Characteristics
Mild	1	Mildly diminished radionuclide localization with preservation of the cortical margins
Moderate	2	Moderately diminished radionuclide localization with partial loss of cortical margins
Marked	3	Markedly diminished radionuclide localization with complete loss of cortical margins

TABLE 3
Number and Severity of Lesions Detected

	Grade 1 (%)	Grade 2 (%)	Grade 3 (%)	Total
Total no. of lesions	64	157	49	270
Identified by GH	63	149	49	261
Missed by GH	1	8	0	9
Identified by MAG3	37	117	47	201
Missed by MAG3	26	32	2	60

TABLE 4
Match and Mismatch Lesions by Grade of Severity

	Grade 1 (%)	Grade 2 (%)	Grade 3 (%)
Match	57 (36/63)	73 (109/149)	96 (47/49)
Mismatch (missed by MAG3)	41 (26/63)	21 (32/149)	4 (2/49)
Reverse mismatch (missed by GH)	2 (1/63)	5 (8/149)	0

Numbers of lesions are indicated in parentheses.

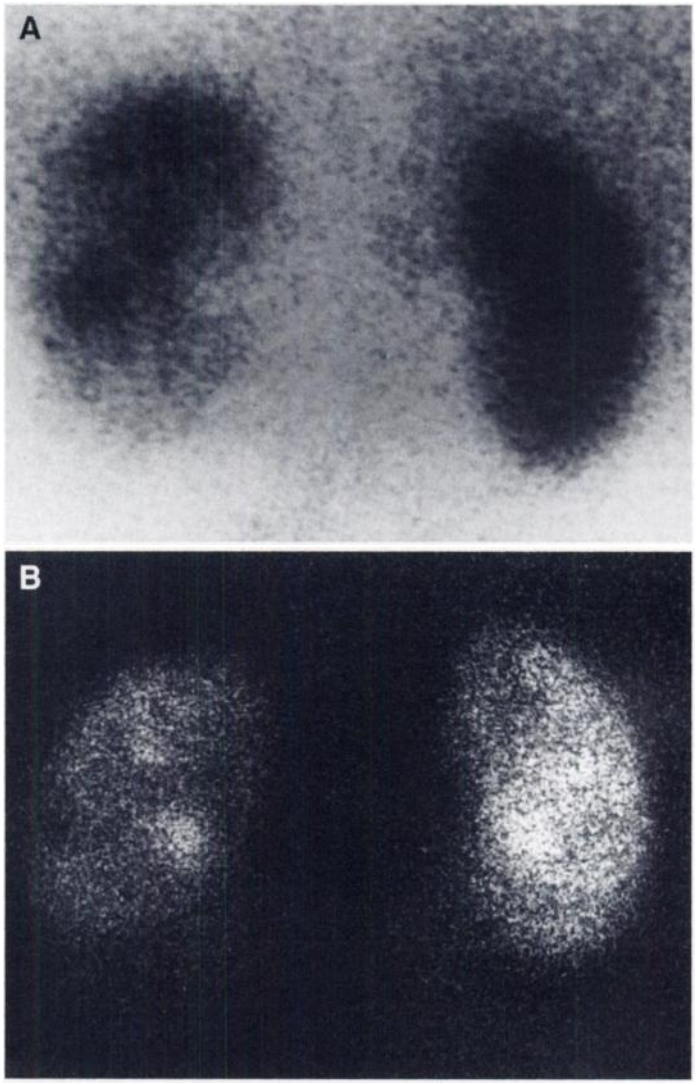

FIGURE 2. Multiple cortical lesions identified by (A) MAG3 and (B) GH studies.

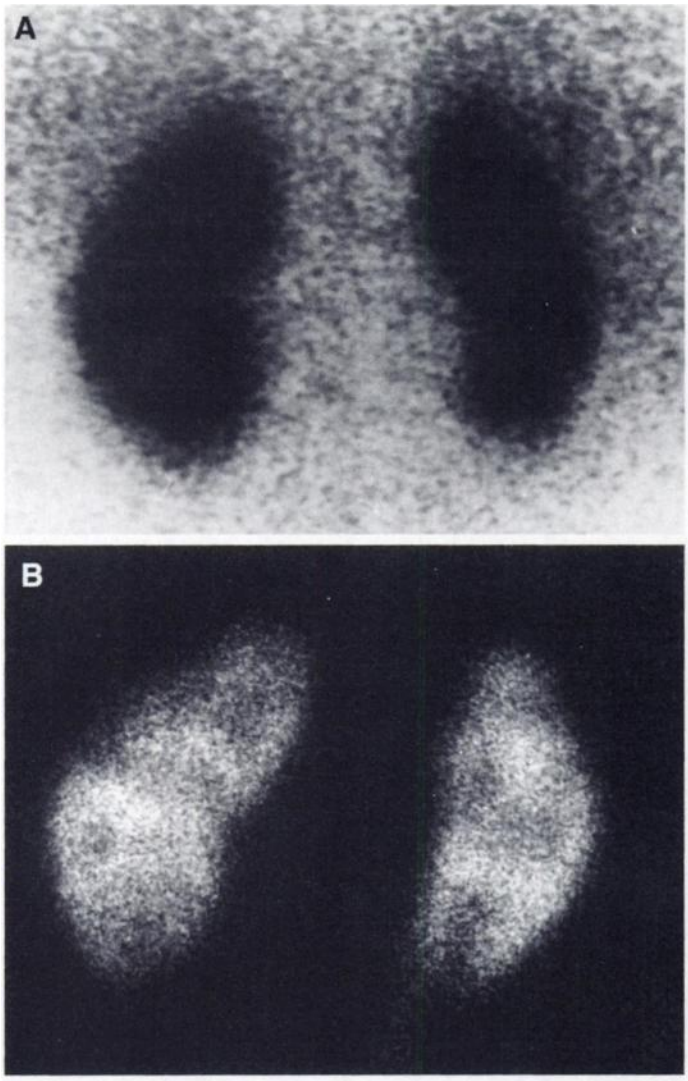

FIGURE 3. (A) Normal MAG3 study. (B) Multiple lesions of Grade 1 and Grade 2 identified with GH in both kidneys.

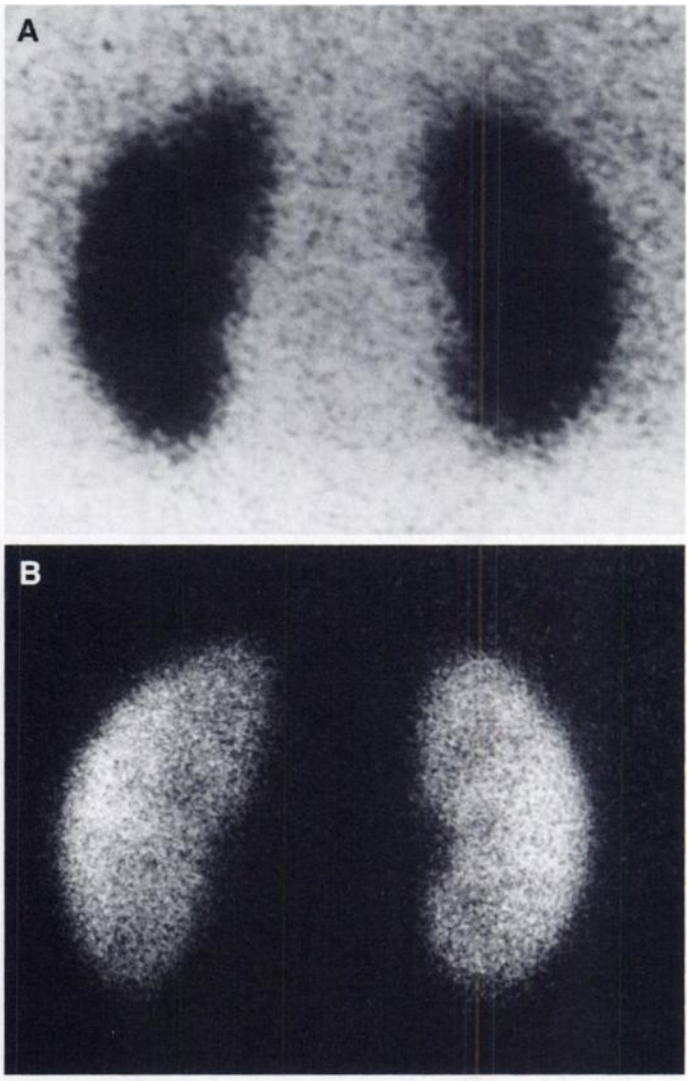

FIGURE 4. Grade 2 lesion in the left upper pole identified in the (A) MAG3 study was not identified by (B) GH scintigraphy.

patients had an acute symptomatic episode with an evolution of <48 hr (Fig. 4).

DISCUSSION

Cortical scintigraphy is the preferred imaging modality to identify renal parenchymal lesions secondary to an infectious process (*1,8,12*). It has an excellent sensitivity to detect decreased or absent radionuclide localization in affected areas. This abnormality is directly related to an alteration in cellular function and the inflammatory response elicited by the infectious process, resulting in diminished radionuclide delivery and localization to the affected area (*5,8*). Changes at the microcellular level frequently escape the resolution of the more commonly used radiographic modalities, because these depend on significant macrocellular anatomical changes, hence the low sensitivities reported in the literature for these studies in evaluating pyelonephritis (*1,8*).

At present, GH and DMSA are the agents available to perform cortical scintigraphy. MAG3 is a tubular agent that allows the evaluation of renal physiology: perfusion, early cortical phase (where 80% of the radionuclide is localized by the tubules) and excretory function. The early cortical image is comparable to the delayed posterior GH scintigraphy, as both reflect tubular localization. Thus, it is not surprising that the cortical abnormalities seen with GH can also be recognized with MAG3.

Our study reveals that MAG3 scintigraphy can detect 75% of the cortical lesions secondary to pyelonephritis. Its sensitivity to recognize lesions depends on their severity. The use of a grading system has been helpful in the characterization of the cortical lesions. We propose its regular utilization in the interpretation of cortical images.

CONCLUSION

These results document that MAG3, in the early phase of the study (1–2 min), can detect Grade 2 and Grade 3 lesions, but it is less effective in detecting Grade 1 abnormalities. This difference in detectability may be related to technical disadvantages of the early MAG3 images, which have limited ability for magnification. In addition, MAG3 dynamic images are of low counts. These two factors determine whether high-resolution images can be obtained to evaluate parenchymal changes.

The reverse mismatch phenomenon on the MAG3 scintigraphy provided additional information not obtained by GH images in 4% of acute pyelonephritic lesions. In these cases, the studies were performed within 48 hr after symptomatology started. We believe that this phenomenon is probably related to a slow and progressive localization of the radionuclide in the affected area, resulting in a normal GH image in the presence of infection (*13*). These lesions would have been missed in the GH study without a preceding MAG3 study, suggesting that the pathophysiologic and biochemical changes related to the infec-

tive process are, indeed, complex. Our data document that MAG3 early cortical images can be used to detect cortical lesions related to pyelonephritis, although they cannot replace GH images. The combination of both studies can improve the detection of acute parenchymal infection.

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Prediction of Urinary Excretion of Technetium-99m-MAG3

Charles D. Russell, Eva V. Dubovsky and Andrew T. Taylor, Jr.

University of Alabama Hospital and VA Medical Center, Birmingham, Alabama; and Emory University Hospital, Atlanta, Georgia

The urinary excretion of ^{99m}Tc-mercaptotriacetylglycine (MAG3), like that of ^{131}I-orthoiodohippurate (OIH), can be used to identify acute renal transplant rejection and measure its severity. This parameter is often quantitated as the excretory index (observed excretion/predicted excretion). A new method for predicting the urinary excretion of ^{99m}Tc-MAG3 is presented. **Methods:** The expected excretion was calculated from multisample plasma time-activity curves in 122 subjects, with correction for the first pass of the initial bolus. The resulting formula was tested prospectively against actual urine measurements in an additional 466 subjects. **Results:** Least-squares fitting led to the following equation:

$$\text{Predicted excretion} = 0.79(1-\exp(-0.0066C_{MAG3}),$$

with residual s.d. 0.06, where C_{MAG3} is MAG3 clearance in ml/min and the predicted excretion is expressed as a fraction of the administered dose.

Tested prospectively in the additional 466 subjects, the s.d. was 0.09. **Conclusion:** A new formula to predict the urinary excretion of ^{99m}Tc-MAG3 has been developed and prospectively validated. Based on our data, the normal range for the excretory index using MAG3 is the same as that of ^{131}I-OIH, 0.8–1.2.

Key Words: technetium-99m-mercaptotriacetylglycine; kidney transplant; kidney function; transplant rejection

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The urinary excretion rate of the tubular agents ^{99m}Tc-mercaptotriacetylglycine (MAG3) and ^{131}I- or ^{123}I-orthoiodohippurate (OIH) has been useful in the diagnosis of acute transplant rejection as well as in monitoring the severity of rejection and the response to immunosuppressive therapy (*1–9*). When acute rejection occurs, the actual excretion (measured directly by counting the voided urine) falls below the predicted value. This change results from retention of activity in the renal parenchyma, which is easily seen on gamma camera images in severe cases. Parenchymal retention can be evaluated subjectively by inspection of the images, but for many years we have preferred quantitative to subjective analysis. At our clinic, the preferred means of following this indicator of rejection has been the measurement of urine excretion, expressed as the excretory index (EI) (observed excretion/predicted excretion). In the past, the expected excretion for MAG3 has been calculated from an empirical formula based on 28 patients (*6*). Here we present an improved formula for predicting the urinary excretion of MAG3 based on multisample clearance measurements in 122 subjects.

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For correspondence or reprints contact: Charles D. Russell, MD, PhD, Division of Nuclear Medicine, 619 South 19th Street, Birmingham, AL 35233.

MATERIALS AND METHODS

Patients

Two groups were studied. The formula for renal excretion was derived from the first group (Group A) and then prospectively tested against the second group (Group B).

Group A. Multisample plasma clearance curves were measured in 154 consenting adult subjects from several centers (*10,11*): the University of Alabama Hospital, Birmingham, Alabama; the Veterans Administration Medical Center, Salt Lake City, Utah; Emory University Hospital, Atlanta, Georgia; St. Joseph's Health Center, London, Ontario, Canada; and by courtesy of Dr. Amnon Piepsz, from several sites in Belgium. After computer screening for quality control, as described later, 122 plasma curves of high quality remained for final analysis.

Group B. To test the equation, urinary excretion was measured in 466 subjects for whom significant retention of activity in renal parenchyma or collecting system could be excluded. Specifically excluded were patients having images that showed retained activity that would interfere with accurate measurement of excreted activity, retained either in the renal parenchyma (acute rejection or acute