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

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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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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

tubular necrosis) or in the collecting system (obstruction or dehydration). Chronic rejection is not associated with abnormal parenchymal retention until end-stage renal disease (*1*). The exclusions were necessary to (a) compare measured with predicted excretion and (b) create a reference curve for patients with no retention so that retention in any patient can be measured by deviation from the reference curve. The following groups comprised the study population: (a) normal transplant donors (preoperative, n = 410; postoperative, n = 13); (b) transplant recipients with normally functioning grafts (n = 14); and (c) transplant recipients with chronic rejection (n = 29). The clinical classification was based on chart review.

Experimental Measurements

Group A. The measurements consisted of plasma activity (expressed as percentage of administered dose per liter of plasma) and corresponding sample times (time after intravenous injection of ^{99m}Tc-MAG3) for at least six samples per patient, typically eight samples spanning the interval from 5–10 min to 90 min after injection.

Group B. The measurements were made by the clinical protocol used routinely at the University of Alabama and described in the literature (*8*), which included urine collection at 35 min after injection and correction of the voided activity for postvoiding residual bladder activity as measured from prevoiding and postvoiding gamma camera images. MAG3 clearance was calculated from a single timed plasma sample (*10*), and extravasation of the dose was excluded by imaging the injection site.

Data Screening (Group A Only)

The data were screened by an operator-independent quality control program as described previously (*10*). In brief, the datasets were each required to fall on a smooth curve and to have s.d. for the estimated MAG3 clearance of no greater than 20 ml/min. After screening, 122 datasets of high quality remained.

Data Processing (Group A Only)

The multisample plasma clearance data were fitted to a biexponential curve using standard methods (*12*), fitting the plasma time-activity curve by nonlinear weighted regression using the program NL2SOL (*13*) with weighting for constant percentage error. (This weighting assumes that the dominant errors arise in laboratory manipulations and not in Poisson counting error, so that the s.d. of a measurement is proportional to the measured value.) From the fitted parameters, expected excretion at 35 min was calculated as described by Matthews (*14*) and by Tauxe et al. (*15*). (There is a sign error in Tauxe et al.'s transcription of Matthews's formula.)

Correction for First Pass of Injected Bolus. Excreted activity is the sum of the excretion predicted by the compartmental model plus the activity excreted on the first pass of the injected bolus before the tracer distributes in body compartments. When calculating excretion using the compartmental model, the effective dose is that remaining after subtracting the activity excreted on the first pass. The activity excreted on the first pass is simply the extraction fraction for the tracer (0.53 for MAG3) (*16*) × the fraction of cardiac output received by the kidneys × the administered dose. The fraction of cardiac output received by the kidneys is normally 20%. For patients in whom MAG3 clearance was lower than normal, we assumed that renal blood flow (as fraction of cardiac output) was proportionally lower.

RESULTS

Figure 1 shows a plot of the predicted excretion (with correction for the first pass of the injected bolus) versus MAG3 clearance for all 122 subjects. Also shown is the fitted curve, which corresponds to the following equation:

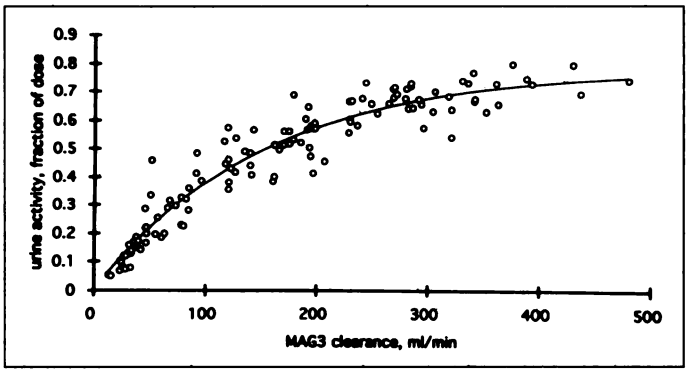

FIGURE 1. Predicted excretion versus MAG3 clearance with fitted curve.

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

Here, C_{MAG3} is the MAG3 clearance in ml/min and the predicted excretion is expressed as a fraction of the administered dose. The residual s.d. from the fitted curve was 0.06 (in dimensionless units, as a fraction of dose administered). This curve is of the mathematical form used by Tauxe et al. for OIH (*17*), but the parameters have been adjusted for best least-squares fit to the current MAG3 data.

Figure 2 compares this equation with directly measured urine activity in 466 subjects, plotting measured urine excretion (as fraction of injected dose at 35 min) against MAG3 clearance. The measured values can be seen to agree well with the predicted values. (Of 466 measurements, 5%, or about two dozen, were expected to lie outside the 95% confidence limits, as was observed). The s.d. of the prospective measurements was 0.090. Direct fitting to this second set of data yielded a s.d. of 0.087, no significant gain over the formula being tested. The s.d. is greater than that for Group A, presumably because of errors associated with the measurement of urine activity and with using a single-sample rather than multisample method for effective renal plasma flow. Since these errors will also be present in clinical use, the normal range is 0.82–1.18 (2 s.d. from the expected value of 1.00). Of Group B, using the routine clinical procedure, there were 410 measurements in the normal subjects, so that the normal range was well defined. The remaining 56 measurements verified the accuracy of the curve when renal function is impaired.

The effect of the bolus correction was small. With bolus correction, the parameters in the equation were 0.79 ± 0.02 (estimate and s.d.) and 0.0066 ± 0.0004; without correction, the parameters were 0.75 ± 0.02 and 0.0066 ± 0.0005. The bolus effect is larger in the case of OIH because of the larger extraction fraction. We, therefore, tested the effect of the bolus correction on a set of 69 OIH clearance curves from a previous

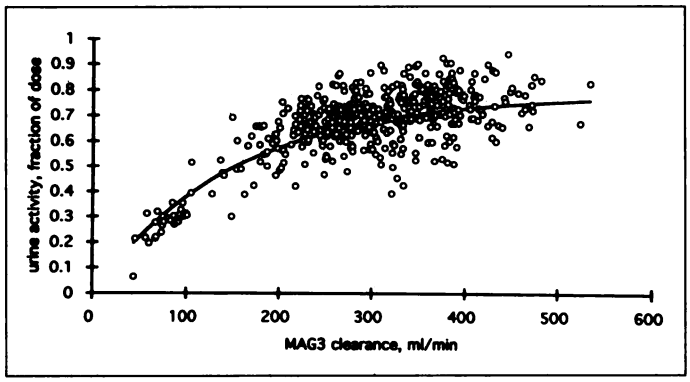

FIGURE 2. Measured excretion versus MAG3 clearance with predicted curve from Figure 1 (prospective test of fit).

study (*18*). With correction, the calculated parameters were 0.78 ± 0.02 and 0.0050 ± 0.0004, in complete agreement with the parameters measured by Tauxe et al. (*17*) from direct urine sampling (0.79 and 0.0048). Without the correction, the parameters differed significantly, 0.071 ± 0.02 and 0.0053 ± 0.0005. Apparently, the correction, though slight in the case of MAG3, is justified.

DISCUSSION

Acute transplant rejection has been monitored routinely since 1975 at the University of Alabama by measuring the urinary excretion of ^{131}I-OIH or ^{99m}Tc-MAG3 and then comparing observed with predicted excretion by means of an EI, defined as the ratio of observed to predicted excretion (*1*). (Figs. 1 and 2 show not the EI but rather the denominator of the EI; the numerator is the directly measured activity in the voided urine). A low EI (<0.8) indicates that activity has left the blood without appearing in the voided urine; inspection of gamma camera images will reveal whether the missing activity is in the parenchyma or in the collecting system. In the absence of obstruction, dehydration or dilatation of the collecting system, which usually can be recognized from the images, the EI provides a quantitative measure of parenchymal retention that serves to detect and monitor acute rejection. The EI will show whether retention is abnormal. The images confirm whether the abnormal activity is in the parenchyma (acute tibular necrosis or acute rejection) or in the collecting system (obstruction or dehydration). The mechanism underlying the parenchymal retention is believed to be a fall in urine flow resulting from a fall in glomerular filtration rate, impairing washout of the activity secreted by the tubules. The EI can thus be regarded as an indirect measure of filtration fraction. This holds only for tubular agents (^{99m}Tc-MAG3 or ^{131}I/^{123}I-OIH) and not for glomerular agents such as ^{99m}Tc-diethylenetriaminepentaacetic acid (DTPA). Also note that the index is useful only in the management of transplanted kidneys. (At the University of Alabama, the EI is calculated for all patients undergoing renography, but for nontransplant patients, it is used only for quality control as a check on the laboratory measurement of MAG3 clearance. Values greater than 1.2 indicate laboratory error, and values less than 0.8 should be explicable on inspection of the images by observing retained activity in either the parenchyma or collecting system.)

Low EI and low filtration fraction (with parenchymal retention on the images) are hallmarks both of acute tubular necrosis and of acute rejection, and there can be no distinction between the two diagnoses if measured only once. With serial measurements, however, the distinction can be made from the time course of EI and of MAG3 clearance. At the University of Alabama, a baseline study is performed routinely within 2 days of transplantation. Acute tubular necrosis will be present on the baseline study and will resolve with time. Any deterioration of the quantitative indexes after the baseline study or a change in an improving trend indicates acute rejection rather than acute tubular necrosis. The question of cyclosporine toxicity, if it arises, is not so easily resolved. Our clinical impression is that depression of EI by cyclosporine toxicity is usually small, so that a distinct fall in EI is more characteristic of acute rejection, but this is hard to document.

After changing from ^{131}I-OIH to ^{99m}Tc-MAG3 for routine renography, we found that normal transplants sometimes had EI values as low as 0.7 (*9*) in contrast to our previous low normal of 0.8 for OIH (*5*). This can now be explained as the result of inaccuracy in our earlier formula for predicting the renal excretion of MAG3, published in 1988 on the basis of only 28 patients (*6*). That older formula should be replaced by the one presented here, now based on 122 subjects from multiple centers. The normal range found in this study was 0.82–1.18 for MAG3, unchanged from the range of 0.8–1.2 previously used for OIH.

CONCLUSION

The EI (observed excretion/predicted excretion) is recognized as a useful parameter in identifying acute renal transplant rejection. The formula presented here for predicting the urinary excretion of ^{99m}Tc-MAG3 is based on data from 122 subjects. It has been validated prospectively and should replace the one we published in 1988 (*6*).

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