Teaching Editorial

The Principles and Technical Aspects of Diuresis Renography

It is intuitive that dilatation of the urinary tract is most likely caused by obstruction. However, the opposite is more often true. That is, dilatation is not associated with obstruction, especially in children. The most common causes for hydronephrosis and hydroureter include infection, vesicoureteral reflux, congenital megacalyces and megaureter, previous obstruction, and bladder noncompliance.

The extent of obstruction can be a spectrum from minimal to total. The degree of hydronephrosis in this spectrum may be variable and may even be absent in total obstruction (*1, 2*). The function of the kidney in obstruction also is variable. In individuals with partial obstruction, the condition is often unsuspected with symptoms from the obstruction occurring only during episodes of diuresis (*3*).

Theoretically, one can consider obstruction on the basis of its significance, which is that there may be a loss of renal function with time. The exact mechanism for renal function loss is not known, but it may be related to increased intrapelvic back pressure with subsequent ischemia and atrophy of renal cells. Poor development of the renal cells may occur in the obstructed immature kidney. Thus, obstruction may be more devastating in the fetus and newborn. Direct reabsorption of toxic materials also may contribute to the loss of function.

Techniques such as intravenous pyelography and ultrasonography, which anatomically document the degree of dilatation of the urinary tract, cannot quantitatively determine the presence of obstruction or its significance. Radionuclide renography more readily quantifies abnormal renal function. Serial renographic studies with furosemide (*4*) can document renal function loss and, thus, determine the significance of the obstruction. Diuresis renography with furosemide (*4*) provides an objective quantitative means for determining the renal function changes over time.

PRINCIPLE OF DIURESIS RENOGRAPHY

The principle of diuretic renography is to challenge the dilated collecting system with a physiologic bolus of urine in order to determine the rate of clearance of the radioactivity from the collecting system. Diuretic renography should have evidence that there is: (1) retained radionuclide within the collecting system; (2) sufficient renal function to promote an adequate diuresis; (3) adequate hydration of the patient; and (4) a bolus response of urine to wash out the dilated collecting system. Theoretically, the ideal radiopharmaceutical, therefore, should be rapidly and completely cleared from the blood; the patient should be well hydrated; the patient's kidneys should be able to respond adequately to the diuretic; and one should have the capability of quantitatively determining the clearance of the radioisotope from the upper tracts. The diuretic response is recorded as the clearance half-time determined from a region of interest (ROI) over the dilated urinary tract. The clearance half-time is expressed in terms of minutes following the diuretic injection. It can also be expressed as the slope of the clearance response. The shape of the washout curve provides only a subjective analysis of the diuretic response.

TECHNICAL ASPECTS

Since the initial report on diuresis renography by Rado (*5*) in 1968 there have been many reports on the use of this technique (*6–23*). The protocol consists of two phases: renogram and diuresis.

Renogram Phase

1. Patients are given Lugol's solution prior to examination if radioiodinated orthoiodohippurate (OIH) is used.
2. Intravenous hydration is given prior to and during the study (*21,22*).
3. Patients with a paralytic bladder should be catheterized and the catheter left open to drainage during the diuresis. Catheterization of infants and untrained children is recommended (*24–26*).
4. Technetium-99m-DTPA is administered intravenously, 100 μCi/kg. Angiographic images are recorded at 4-sec intervals for 12 images. Subsequent one-minute images are recorded for five minutes.
5. Iodine-131 OIH, 100 μCi, is administered intravenously. Computer frames at 15-sec intervals are recorded for 30 min. Analog images are recorded after the 2-min, 3-min, and then 5-min intervals for 30 min.

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6. Patients are asked to void and then are repositioned on the gamma camera. If the bladder is full, then catheterization should be considered.

Diuresis Phase

7. Computer frames at 15-sec intervals are recorded for 20 min. Five-minute static images are recorded for 20 min. Furosemide at 1 mg/kg is given intravenously at 2 min into the study.
8. The clearance response is calculated by monitoring a ROI over the dilated renal pelvis or ureter. The half-time clearance response is determined from the injection at 2 min until one-half of the activity remains in the ROI.
9. A final ^{99m}Tc image is obtained, which includes the kidneys, ureter and bladder.

THE CLEARANCE RESPONSE

There is a consensus that a clearance half-time of between 3 and 7 min is expected in the normal nonobstructed urinary tract while a clearance half-time of >20 min is typical of an obstructed urinary tract (Fig. 1A–C). Since obstruction may be a spectrum, which varies between no obstruction to total obstruction, the response will also reflect this spectrum. In a clinical setting, many responses are in an intermediate range, that is, a clearance half-time of between 10 and 19 min.

As with all medical tests, the interpretation and the accuracy of that interpretation is dependent upon a knowledge of the principles involved and clinical experience. In the presence of *good renal function*, there is little difficulty with the interpretation of a normal or, conversely, an obstructed urinary tract. The finding of an intermediate response poses greater difficulty for a correct interpretation. Serial studies are often of greater value in the analysis of a given clinical condition. A clearance half-time, which increases from one study to the next, indicates either an increasing obstruction or, more importantly, worsening of the patient's renal function. A worsening of renal function due to obstruction by definition means a significant obstruction. The diuretic renogram, therefore, can serve as a management tool as noted in Table 1.

TECHNICAL CONSIDERATIONS

There are technical and physiologic principles of diuretic renography, which must be understood in order that interpretation of the study be as reliable as possible. Included among these are the following nine principles.

Renal Function

There must be adequate renal function for the kidney to respond with a diuresis. End-stage renal disease or conditions, which principally affect the tubules such as acute tubular nephropathy, will produce little, if any, diuretic response and, thus, an abnormal clearance half-time may occur without obstruction. The rate of accumulation of radionuclide during the second phase of the renogram curve indicates the functional ability of the tubules of the kidney and helps to determine if the diuretic response is meaningful. The intensity of localization of the radionuclide in the parenchyma of the kidney as depicted on a 2-min image can also serve as a good indicator of renal function. If the diuretic is administered when there is evidence of markedly diminished renal function, then any clearance response in that circumstance will diminish the probability of obstruction as a cause for the poor function. In such a circumstance, serial studies to determine the stability of renal function is essential. An improving or unchanged response will by definition exclude significant obstruction.

If renal function is extremely poor, i.e., the kidneys only faintly visualize on the 5-min ^{99m}Tc-DTPA image, then ^{131}I-OIH should not be administered. Poor ^{131}I-OIH clearance will give the patient an unnecessary high absorbed radiation dose. A Whitaker test may be more appropriate in this circumstance.

There is now evidence to suggest that renal function and especially the response to a diuretic is compromised in the newborn period (0–3 mo). Koff and associates reported that 68% of normal kidneys when studied with diuretic renography before one month of age had half-times of more than 9 min (*27*). When studied between 1 and 4 mo, 33% of nonaffected kidneys had a half-time of more than 9 min. All children older than 4 mo had a normal half-time in the nonaffected kidney. Importantly, all premature infants exhibited abnormal half-times in the first month of life, whereas, only 55% of full-term infants had abnormal studies. The children were not catheterized for these studies. From these data, it would seem prudent to delay the functional diuretic renogram study for a month or two after birth. If the study is performed and the nonaffected kidney demonstrates an abnormal response, then the interpretation of the results of the affected kidney must be couched in terms which recognizes the functional immaturity.

On occasion, the diuretic response will have an unusual appearance. Normally the clearance slope will begin within 2–3 min following administration of the furosemide (*9,10*). For unknown reasons, the response may be delayed for 6–10 min (Fig. 2A–C). Several reasons are postulated as being causative:

1. The diuretic may be injected subcutaneously rather than intravenously.
2. There may be underlying tubular disease, and the diuretic response is compromised.
3. Time may be needed to build up the necessary intrapelvic pressure to overcome a partial obstruction.
4. The distensibility of the renal pelvis may be such that it easily accommodates the extra fluid before it can drain into the ureter.

Conversely, one may see a reasonable response for a short interval only to have the response plateau (Fig. 3). It is postulated that there is a build-up of intrapelvic pressure by the diuresis which is sufficient to temporarily overcome a partial obstruction. Thus, when sufficient fluid is drained, the pressure drops to levels which are once again obstructive.

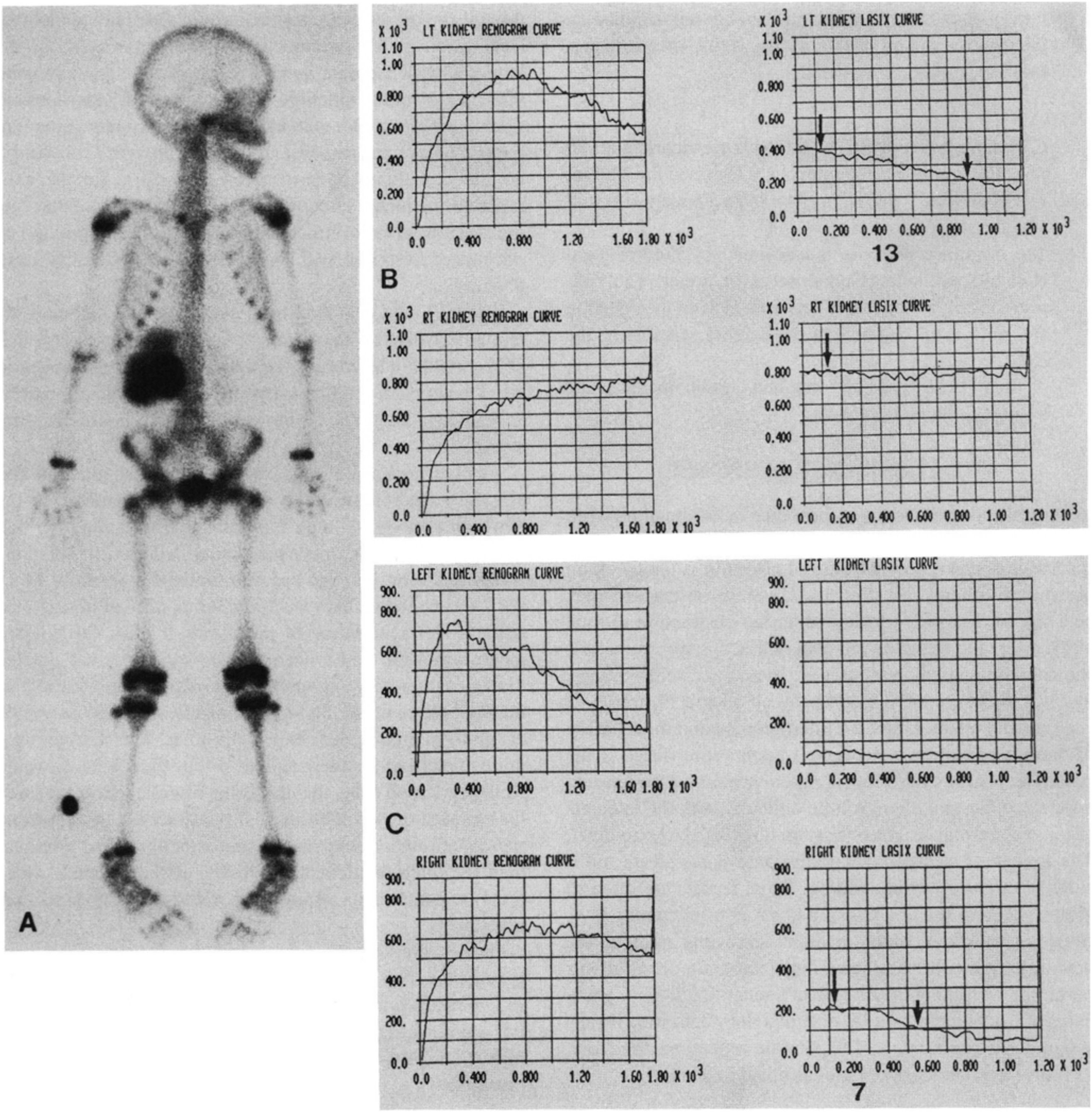


FIG. 1. A markedly hydronephrotic right kidney was noted on bone scintigraphy (A) at 3 hr. This 6-yr-old child was completely asymptomatic for urinary tract disease. Diuretic renography with ^{131}I-OIH and 1 mg/kg furosemide (B) demonstrated no response in the right kidney. There is an intermediate response in the left kidney even though no hold up is noted on the bone scintigram at 3 hr. After pyeloplasty of the right kidney, the clearance half-time is 7 min (C). The clearance of the left kidney has also improved without surgery. This phenomenon is a common observation following unilateral pyeloplasty for obstruction. The mechanism is unknown.

These variations in the diuretic response pose a problem in the interpretation because the half-time clearance may be abnormal even when the principal slope of the response is essentially normal. The referring physician should be alerted to these unusual responses.

Of importance, the Whitaker test (*23*) is independent of function. The standard volume of fluid administered during the Whitaker test is 10 ml/min. The pressures recorded are categorized into a normal range, an intermediate range, and an obstructive range. A similarity in categories is noted between the Whitaker test (pressures) and diuresis renography (clearances) when comparisons are made between patients. Importantly, it has been shown that the volumes of urine attained by diuresis during diuretic renography can achieve 20–25 ml/min (*28*). The diuretic response and its duration depends upon the patient's tubular function, state of hydra-

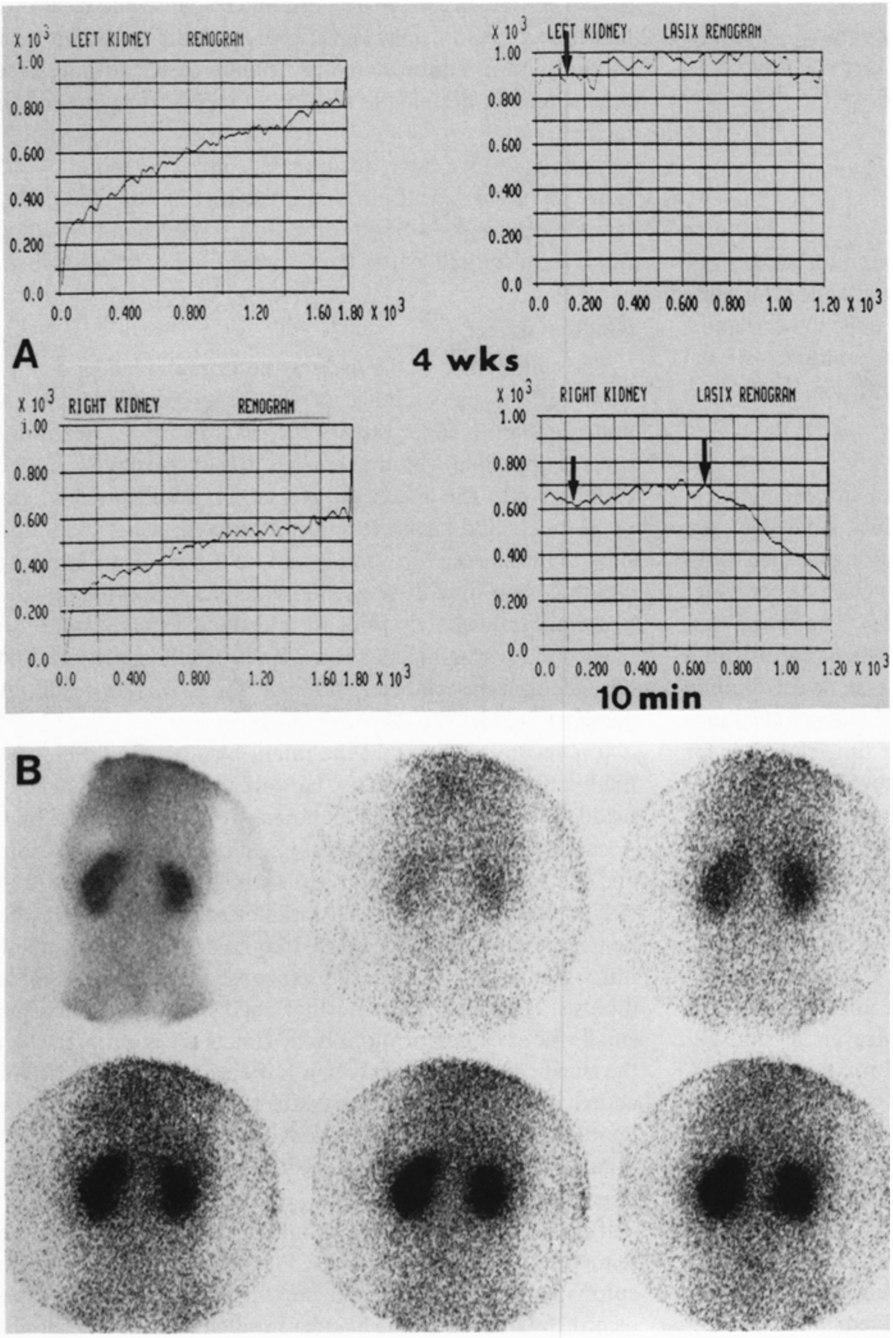
TABLE 1. Diuretic Renogram

Response	Clearance half-time	Management
Normal	0–9 min	Routine follow-up (1 yr)
Intermediate	10–19 min	Early follow-up (4–6 mo)
Obstruction	20+ min	Immediate intervention

tion, the administered dose of diuretic, collecting system compliance, and perhaps other factors still unknown. Be that as it may, both the Whitaker test and diuretic renography have an accuracy between 58% and 86% (*24,25,29–32*) in predicting histologic obstruction.

Volume Effect

The volume of hydronephrosis affects the clearance half-time (*33*). The clearance of any indicator varies directly with the rate of fluid flow through the reservoir and inversely with the volume of the reservoir (*34*). In the presence of a marked hydronephrosis one may expect that the diuretic response will have a diminished effect upon clearance half-time. For example, if a markedly hydronephrotic collecting system containing 150 ml of radioactive urine is flushed with 10 ml of nonradioactive urine per minute, it will require 11 min just to clear 50% of the radioactivity even when there is no obstruction. The clearance half-time will be even more prolonged if the urine produced during diuresis is radioactive. This provides an argument against the early injection of the



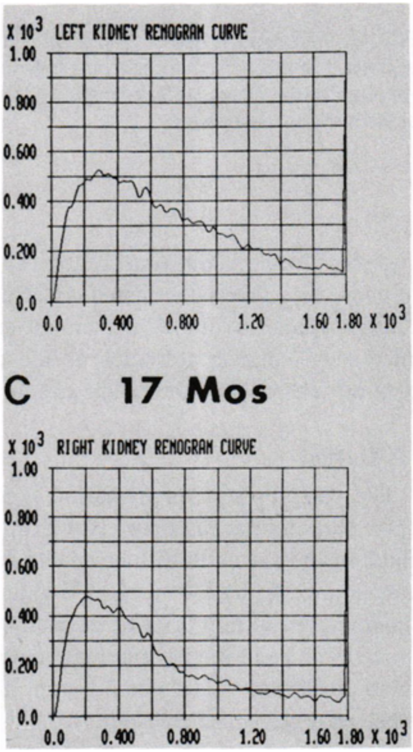


FIG. 2. There is a delayed response of 10 min in the right kidney (A) in this 4-wk-old infant. There is a poor response in the left kidney, which was hydronephrotic on ultrasound examination. The ^{99m}Tc-DTPA five-minute image and the ^{131}I images (B) demonstrate marked retention of the radionuclide in both collecting systems. Follow-up study at 17 mo of age after unilateral pyeloplasty of the left kidney (C) demonstrates almost normal bilateral drainage.

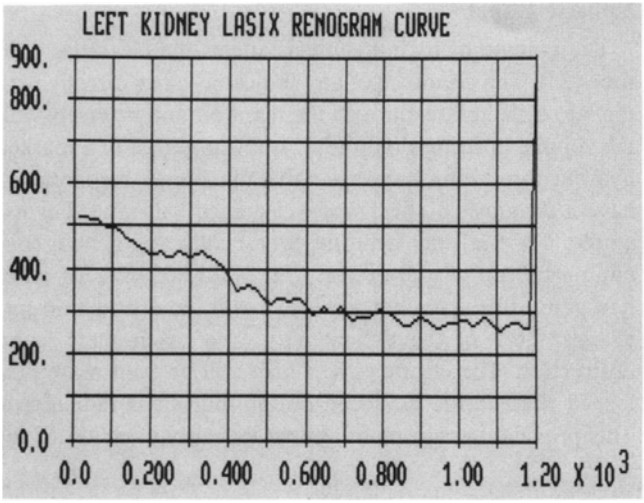


FIG. 3. Plateauing is noted after an initial response to furosemide diuresis. The mechanism for this phenomenon is not understood. Of importance, the clearance half-time is >30 min, but the initial slope of the curve is reasonable.

diuretic. Therefore, one must cautiously interpret the diuretic response in a markedly dilated collecting system. The same caution applies to the Whitaker test as well. Other factors affect the Whitaker test such as the concentration of the contrast material and the needle size for infusion (*35*).

Hydration

The patient's state of hydration has an important effect upon the diuretic response. Howman-Giles studied eleven children and one adult with normal hydration and then again after administering 360 ml of 0.9% sodium chloride per meter squared over 30 min prior to the study (*21*). The mean half-time clearance in the normal renal units was 6.0 min with a standard deviation (s.d.) of 3.1 min. The standard diuretic renal study was considered abnormal if the half-time clearance was >15.3 min ($\bar{x}$ + 3 s.d.). The mean half-time clearance for the normal volume expansion hydrated renal study was 3.9 min with a s.d. of 2.1 min. The study was considered abnormal if the half-time clearance was >10.2 min ($\bar{x}$ + 3 s.d.). Ten of the twelve patients' studies went from an abnormal range to the normal simply because of adequate hydration. Of course, forced hydration is not the normal physiologic state, but it does point out that the state of hydration may affect the quantitative response and subsequent interpretation. All patients, therefore, should be given an intravenous infusion of 0.9% sodium chloride (*21*) or a 50:50 mixture of 0.45% sodium chloride and 2.5% glucose and water prior to the diuretic challenge (*18*). Other formulae for hydration have been suggested (*26*). Nurnberger (*28*) reported that the kidney may excrete as much as 20–25 ml/min in response to the diuretic. Such volumes are well in excess of the standard 10 ml/min, instilled during the Whitaker test. Lupton (*36*) has indicated that 10 ml/min may cause some cases with potentially obstructive hydronephrosis to be missed.

Dose Response

In their original report on the technique of diuretic renography, O'Reilly, et al. recommended an administered dose of 0.5 mg/kg of furosemide (*7*). Several authors (*8,10,11*) have subsequently recommended 0.3 or 0.5 mg/kg with an upper limit of 40 mg.

It should be noted that the response to furosemide is dose-dependent. That is, one will observe a better response with 1 mg/kg than with 0.5 mg/kg. Furosemide is also a relatively safe drug and nephrologists have used even larger administered doses without adverse effects. We have, therefore, opted to use 1 mg/kg to ensure the likelihood of an adequate response. Also, limiting the total administered dose to 40 mg does not seem to make much sense. The volume distribution of 40 mg in a 300-pound individual surely cannot be the same as in a 90-pound person. The diuretic response and clearance half-time, therefore, may be variable depending upon the dose of furosemide administered. A standardized administered dose should be adopted to obviate variable results due to this factor.

Since 1978, we have documented only two minor "reactions" to furosemide. Both were episodes of feeling faint. One episode occurred ~4 hr after the study. We recommend that fluids be given freely after the test when not contraindicated.

Bladder Effect

The compliance of the ureters and urinary bladder significantly affects the drainage of the upper urinary tracts. A noncompliant bladder rapidly increases its intravesical pressure as the fluid volume exceeds the distensibility of the bladder wall. The increased pressure is transmitted to the upper tracts and back pressure will impede the diuresis and slow the clearance. The result will be a prolongation of the clearance half-time. It is essential, therefore, that the bladder be empty immediately prior to injection of the diuretic. An older child whose bladder has a small fixed capacity should have continuous catheter drainage for a correct result. A paralytic bladder should also be catheterized.

It is recommended that the infant bladder should be routinely catheterized (*24,25,26*). However, the infant has a reflex bladder which will empty spontaneously in response to filling. A catheterized bladder is hardly a normal physiologic state and the results of such intervention may not reflect the true circumstances in life. Do the risks of catheterization in the newborn outweigh the benefits? In our experience, only a few infants have not voided spontaneously during furosemide diuresis. If the results are normal, then we have avoided the small risk of catheterization. If the results are abnormal, then the study can be repeated with a catheter in place. The risk of added radiation is small and affects probably <5% of the population studied. On the other hand, the vast majority of infants will not have been subjected to the risk of catherization.

If a catheter is used, it should be clamped during the renogram portion of the study. A drainage response to the emptying of the bladder following the renogram can then be recorded. Drainage of the bladder through the catheter should be as rapid as possible using a syringe if necessary. Emptying can be monitored on the persistance scope of the gamma camera. If there is a good drainage response of the upper tracts to emptying of the bladder, then the diagnosis of noncompliant bladder can be made and furosemide is unnecessary. This provides a good argument against the administration of furosemide prior to or early during the study. We have termed this phase of the study "the draining renogram." The information provided by the draining renogram is very useful to the urologist since it pinpoints the cause of hydronephrosis. A logistical problem is that each patient's study must be tailored to the situation, which can be time consuming and disruptive to the schedule in a busy department.

Radiopharmaceutical Choice

O'Reilly recommended orthoiodohippurate (^{131}I-OIH) as the radiopharmaceutical of choice for diuretic renography (*7*). This choice of radiopharmaceutical is reasonable because orthoiodohippurate is secreted via the tubules and furosemide acts upon the tubules by inhibiting sodium and chloride reabsorbtion. It is also a simple matter to quantitate the clearance half-time response from the renogram curve. Many practitioners, however, use ^{99m}Tc-DTPA for renal imaging without renography. Thus, the monitoring of the diuretic response from furosemide using ^{99m}Tc-DTPA instead of ^{131}I-OIH has become commonplace.

There are several theoretical considerations regarding the choice of radiopharmaceutical for diuretic renography. Among these considerations are:

1. The radiopharmaceutical should be rapidly cleared from the blood in order that nonradioactive urine be used to washout the collecting system. Flushing a hydronephrotic system with more radioactive urine will prolong the clearance half-time. Radioiodinated OIH is the most rapidly cleared radiopharmaceutical approved by the Food and Drug Administration (FDA). Technetium-99m-mercaptoacetyltriglycine (MAG 3) is excreted at a similar rate (*37*) but is not yet approved for routine use. There are four commercially available ^{99m}Tc-DTPA radiopharmaceuticals each of which have differing blood clearance (*38*) and all of which are longer than OIH radiopharmaceuticals. In addition ^{99m}Tc-DTPA is bound by proteins and, thus, one might expect a variable clearance based upon the individual patient's chemical makeup. If quantitation and serial studies are desirable in order to recognize changes in function, then radioiodinated OIH is currently the most appropriate radiopharmaceutical.
2. In recent years, dual-isotope renography and scintigraphy have become more commonly used for the complete evaluation of the urinary tracts. If an inflammatory process is suspected, then a cortical radiopharmaceutical is preferred over ^{99m}Tc-DTPA (*39*). Cortical radiopharmaceuticals are not suitable for diuretic renography. Thus, a radioiodinated OIH radiopharmaceutical is necessary. Radioiodinated OIH usually is administered after the technetium radiopharmaceutical because of collimator and energy resolution considerations.
3. It is probable that ^{99m}Tc-MAG 3 will become the radiopharmaceutical of choice when it is approved for routine use by the FDA. It is secreted by the tubules and the ^{99m}Tc radioisotope label provides high resolution images. The clearance rate of MAG-3 is similar to the OIH radiopharmaceutical (*37*).

Time of Injection

In order to accurately monitor clearance half-time, the physiologic bolus of urine should be as nonradioactive as possible within the practical time limits of the study. Therefore, the diuretic should be injected only *after* the principal clearance of the radiopharmaceutical from the blood. O'Reilly (*7*) reported that injection of the diuretic *prior* to or within the first 5-min of the injection of the radiopharmaceutical will not affect results. Others recommend that the collecting system should be full (*8,12,17,25*). How one determines that the collecting system is full is not well defined. The curve analysis when furosemide is injected prior to the radiopharmaceutical is subjective and is based upon the pattern which is not quantitated.

Theoretically, the early injection of diuretic will affect the normal unobstructed patient in a minimal fashion while the obstructed system will still present with a prolonged clearance. However, the early administration of furosemide will not reduce the number of intermediate results and a large number of patients (the normals) will unnecessarily be given the diuretic. In addition, this method does not objectively quantitate the effect of diuresis. Therefore, it cannot be used in a serial fashion to determine if there is deterioration of response (renal function) due to significant obstruction.

Poor Diuretic Injection

When the diuretic is injected intravenously, a response is recognized usually within 2–3 min. A subcutaneous injection will cause a spurious delayed response.

Appropriate Regions of Interest

In the presence of dilated ureters, one must be concerned with the possibility of distal ureteral obstruction. The ureter can act as a reservoir. Thus, there can be appropriate emptying of the renal pelvis into the dilated ureter in response to the diuretic injection. The distal ureteral obstruction may not be recognized if the clearance of the radioisotope is not monitored over the ureter as well as the kidney. Regions of interest, therefore, should be circumscribed not only over the kidney but also over the ureter when the ureter is dilated.

CONCLUSION

Diuretic renography provides a noninvasive physiologic means to differentiate the spectrum of obstruction of the urinary tracts. Objective quantitative measurements rather than subjective impressions of response bolster its accuracy and clinical usefulness. The response of a kidney to a diuretic stimulus is a measure of renal function which is the parameter one wishes to measure to monitor the long-term effect of partial obstruction. The study can be performed on a frequent basis if necessary with the radiation burden being similar to that of intravenous pyelography.

Diuretic renography is best used as a management tool. In the presence of a normal response, the possibility of significant obstruction is minimal. That patient can be followed at a routine interval. In the presence of good renal function and an empty bladder, an obstructive response warrants immediate intervention. Caution is advised, however, in the interpretation of the study in a neonate. Finally, the majority of symptomatic patients will exhibit an intermediate response. Follow-up studies at 4- to 6-mo intervals will determine the significance of the intermediate response. A lengthening clearance response depicts worsening function, indicating significant obstruction.

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