Radionuclide studies in paediatric nephro-urology

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Abstract

The main tool of radionuclide techniques applied to paediatric uro-nephrology is the quantitation of function, which is an information not easily obtained by other diagnostic modalities. The radiation burden is low. Drug sedation is only rarely needed, whatever the age of the patient. Accurate determination of glomerular filtration rate can be obtained by means of an intravenous injection of Cr-51 EDTA and one or two blood samples. Tc-99m DMSA scintigraphy is an accurate method for evaluation of regional cortical impairment during acute pyelonephritis and later on, for detection of permanent scarring. Tc-99m MAG3 renography is nowadays a well-standardized method for accurate estimation of the split renal function and of renal drainage with or without furosemide challenge. This technique is particularly indicated in uni- or bilateral uropathies with or without renal and/or ureteral dilatation. Direct and indirect radionuclide cystography are two alternative modalities for X-ray MCUG. Their relative place in the strategy of management of vesicoureteral reflux is discussed. © 2002 Elsevier Science Ireland Ltd. All rights reserved.

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1. Introduction

The main tool of radionuclide techniques applied to paediatric uro-nephrology is the quantitation of function, which is an information not easily obtained by other diagnostic modalities. The radiation burden for all these procedures is below 1 mSv and often much lower [1]. It compares favourably to the radiation dose related to intravenous urography, computed tomography (CT) scan and VCUG. Drug sedation is only rarely needed, whatever the age of the patient. A friendly environment, an adequate attitude toward the child, a technologist well-trained for paediatric procedures and involved parents before and during the procedure generally allow good collaboration of the child during the procedure.

2. Glomerular filtration rate

2.1. Tracer and methods

Measurement of GFR can be obtained after a bolus injection of a radioactive tracer exclusively eliminated by the glomerulus, such as Tc-99m DTPA (diethylene-triamine pentaacetic acid) or Cr-51 EDTA (ethylenediamine tetraacetic acid). It has been shown that the plasma disappearance curve of such tracer allows an accurate determination of the glomerular clearance. The drawback of this method is that it necessitates a rather large number of blood samples, in order to define accurately the plasma disappearance curve. In a recent consensus [2] as well as in a guideline produced by the Paediatric Committee of the European Association of Nuclear Medicine [3], two accurate simplified methods have been proposed for clinical routine in children.

2.1.1. The ‘slope-intercept’ method

This method is based on two blood samples taken around 2 and 4 h after intravenous injection of the tracer [2,3]. This is schematically represented in Fig. 1. The accuracy, compared to the multiple blood sample...
technique, has been well demonstrated for clearance values as low as 10 ml/min.

2.1.2. The ‘distribution volume’ method

This empirical method is based on a single blood sample taken at 2 h [4]. This method is valid for children of any age and the results are identical to those of the slope-intercept method (Fig. 2), but this approach is not valid in patients with GFR below 30 ml/min/1.73 m².

For both methods, the relative error, expressed in % of the clearance value, is large in children below 1 month. Normal values have been published [5].

2.2. Advantages of the radionuclide method

Serum creatinine is a poor guide to glomerular filtration rate because it is highly dependent on muscle mass and is insensitive to changes in renal function until glomerular filtration is substantially reduced. Several formulae and nomograms have been established in order to predict creatinine clearance from plasma creatinine concentration, taking the age, sex and body weight into account. The value of these nomograms is controversial, although they are often considered as ‘sufficient for clinical use’: the error in predicting the true clearance can be considerable. Creatinine clearance is a generally accepted method for evaluating glomerular filtration rate, although it is particularly cumbersome and often inaccurate in young children, because of the need of exact urine collections over a given period. Inulin clearance with constant infusion and indwelling catheter is the golden reference but is generally used only for the purpose of research.

It has been shown that Cr EDTA clearance, even using the simplified techniques, offers the double advantage of being a very simple technique, perfectly adapted to the young child and very well correlated to the reference technique.

2.3. Clinical indications

– Evaluation and follow up of overall renal function (hemolytic uremic syndrome, diabetes mellitus, … nephrotoxic drugs).
– Combined to the split renal function obtained from the renogram or from the Tc-99m DMSA studies (see below), it allows an accurate estimation of the single kidney GFR.

3. Cortical scintigraphy

3.1. Tracer and methods

The most appropriate tracer for that purpose is Tc-99m DMSA (dimercaptosuccinic acid). The tracer is taken up by the proximal tubular cells, directly from the peritubular vessels.

The technical aspects of the procedure as well as the field of application have been described in detail in an international consensus on Tc-99m DMSA scintigraphy [6] and in two recent guidelines [7,8]. Images should be acquired 2–3 h after tracer injection. The collimator should be turned side up and the patient should lay on the camera in supine position. High resolution collimator is required. Pinhole views (2–3 mm aperture) may be useful, particularly in infants, but this technology is not universally used. Posterior and posterior oblique views are recommended; anterior view should be performed in horseshoe kidney and in ectopic pelvic kidney. The matrix should be at least 128 × 128. At least 300,000 counts or 5 min counting per image are necessary. There is at the present time no consensus about the usefulness of tomographic images (SPECT) for DMSA scintigraphy in children. When performing SPECT, attention must be paid to the risk of false positive images and to the necessity of heavy sedation in young children.

3.2. Indications

The main reason for performing DMSA scintigraphy is the detection of cortical abnormalities related to urinary tract infection. It is the technique of choice for evaluation of renal sequelae, at least 6 months after the acute infection. It is the most adequate technique for
the detection of renal impairment during the acute phase of infection (Fig. 3) and the detection of the group at risk to develop renal sequelae. Other indications are the small kidney, the duplex kidney, the dysplasia, the multicystic non-functioning kidney, the ectopic kidney, the horseshoe kidney.

3.3. Interpretation, pitfalls

Lesions appear as hypoactive areas. Differentiation between acute lesions which will improve or disappear and chronic lesions (sequelae) is not always possible: a large polar hypoactive area, without deformity of the outlines and with indistinct margins will generally heal; marked localized deformity of the outlines or deformed outlines (volume loss) generally correspond to permanent sequelae.

3.4. Sensitivity and specificity

Compared to ultrasound and intravenous urography, the sensitivity is high, in both acute and chronic pyelonephritis.

Lesions are not specific, since similar lesions can be found in renal abscess, cyst, duplex kidney, hydronephrosis: the combination of ultrasound and DMSA scintigraphy allows a better differentiation between these clinical situations.
In case of marked hydronephrosis, tracer may accumulate into the renal cavities causing difficulties in the interpretation of the cortical images.

3.5. Validation

Experimental studies in animals have validated DMSA scintigraphy as an accurate technique for the detection of both acute infection and chronic lesions. A recent meta-analysis [9] has shown a sensitivity of 84% for a specificity of 88%. Only small histological lesions are missed by the DMSA technique.

3.6. Relative function

Differential renal function (DRF) can be easily calculated whenever DMSA scintigraphy is performed. One should acknowledge the robustness and the reproducibility of this quantitative parameter. Usual normal values are between 45 and 55% uptake for each kidney. By combining DRF with a 51 Cr EDTA clearance, one can obtain an accurate absolute estimate of the individual kidney GFR.

4. Renography

4.1. Tracers and procedure

The ideal tracers for renography are those exclusively excreted by the kidney, without any retention into the renal cells. They allow estimation of two aspects of renal function: the first one is renal clearance, i.e. the capacity of the kidney to clear the tracer from the blood; the second one is excretion, or disappearance of the tracer from the kidney into the bladder. Tc-99m DTPA, filtered by the glomerulus, has been for years the most widely used tracer for that purpose. Tubular excreted tracers, such as Tc-99m MAG3 (mercaptoacetyltriglycine), are eliminated more rapidly and offer the advantage of a higher signal to noise ratio and therefore a more accurate determination of the quantitative parameters of input and output, particularly in infants.

The technical aspects of the procedure (acquisition and processing) appeared in detail in a recent guideline issued from the Paediatric Committee of the European Association of Nuclear Medicine [10].

Shortly, a normal background corrected renogram curve is characterized by an ascending segment, mainly dependent on the clearance of the kidney, a peak around 3 min and a rapidly descending segment, typical for normal excretion.

When dilatation of the collecting system exists, the standard renogram is generally characterized by a continuously rising curve, reflecting poor drainage of the kidney (Fig. 4). In this condition, furosemide should be administered, which increases urinary flow and may distinguish between good, intermediary and poor drainage.

![Fig. 3. Tc-99m DMSA scintigraphy performed during the first days after diagnosis of an acute pyelonephritis. The right kidney (on the right side of the image) is normal: the contours are smooth; there is some normal heterogeneity of tracer distribution, related to the unequal distribution of parenchyma; no defect is seen. The left kidney is abnormal, showing multiple areas of hypoactivity over the whole kidney, with deformation of the outlines of the kidney. This is a typical pattern observed during acute pyelonephritis. These abnormalities may entirely disappear at a late control (which should be performed at least 6 months after the acute phase) but sequelae representing permanent scarring may be observed at that stage.](image-url)
Fig. 4. Schematic representation of a Tc-99m MAG3 renogram. In ordinate the renal activity after correction for background. In abscissa, the time after intravenous injection of the tracer (total duration: 20 min). The left kidney renogram (black dots) is normal: initial ascending part, corresponding to the uptake phase (parenchymal split renal function); maximal activity corresponding to the equilibrium point between what is still coming into the kidney and what is already leaving the kidney; descending phase, corresponding to a good emptying of the kidney. The right kidney renogram (white dots) is abnormal: initial ascending part, almost comparable to the contralateral side, reflecting a perfectly symmetrical parenchymal split renal function; continuous ascending phase, corresponding to a marked stasis within the kidney. It should be undelineed that in no case can this stasis be considered as a criterion of renal obstruction. At that stage, the test should be continued by injecting a dose of furosemide followed by a new acquisition with postmicturition images, which might end up with a valuable emptying of the right kidney.

Some recommendations related to the procedure are essential:
- The child should be adequately hydrated, but intravenous hydration is considered as unnecessary in most of the patients.
- No bladder catheter is necessary in most of the cases. However, one should be aware that a full bladder and a supine position may result in an artificially poor drainage: for that reason, the procedure of diuretic renography cannot be considered as achieved without additional images obtained after micturition and change of child’s position (erect).

The differential function of each kidney (also called relative clearance, split function, uptake function or DRF) is computed from the 1–2 min images, after adequate correction for background activity \([2,10,11]\). The renal activity per kidney, during this time interval, is expressed as a percentage of the sum of the right and left kidney activity, considered as 100%. Normal values of DRF are between 45 and 55%. DRF should be interpreted in clinical context, since values within the normal range may be seen when there is bilateral renal damage.

Absolute determination of the single kidney GFR can be obtained indirectly by combining DRF with an overall clearance measurement (such as 51 Cr EDTA clearance).

The evaluation of drainage should necessary include the postmicturition images (evaluation of the amount of activity still present in the kidney after micturition).

A simple way to evaluate the drainage is to check all images from the beginning of the tracer injection up to the end of the furosemide acquisition, including the postmicturition views. The activity remaining in the kidney at the end of the postmicturition views should

Fig. 5. Example of a direct radionuclide cystography with successive 10-s images. During the beginning of the filling procedure, only the bladder is visualized (images 16–21). Bilateral and persistent reflux up to both kidneys is then clearly seen, beginning from image 22. Active micturition starts on frame 42, while both kidneys are almost empty. There is no active reflux during the micturition phase.
be negligible in order to conclude to a good drainage. Partial drainage or poor or no drainage can similarly be concluded on the basis of the successive images.

Another way to evaluate drainage is to quantify the furosemide curve, for instance by calculating the \( T_{1/2} \) of the curve. This method, which has gained wide acceptance in the USA [12], has several drawbacks, the most important being that no drainage or poor drainage can be observed on the curve while a simple change of position or an emptying of the bladder some minutes later may result in a dramatic renal emptying.

Finally, the best way to evaluate quantitatively the drainage is to calculate the residual renal activity after micturition. This residual activity can either be expressed in % of the 2-min activity and is then called ‘normalized residual activity’ or NORA [13], or as an output efficiency, in other words the percentage of what has entered the kidney which did come out of the kidney after micturition [14].

4.2. Indications

All uropathies, which require evaluation of individual renal function and/or evaluation of the drainage function, at diagnosis as well as during follow up.

4.3. The interpretation of the renographic parameters

On the basis of the renogram, one can conclude that the uptake of the hydronephrotic kidney is normal or impaired and that the drainage is normal or impaired. However, the definition of obstruction, or better, the definition of the risk factors for further renal deterioration—and therefore the operative indications—are still a matter of debate. It is the task of the surgeon to integrate the radionuclide information into a comprehensive strategy. At the present time, only empirical attitudes are available, based on all kinds of combinations of clearance values, quality of drainage and degree of renal dilatation. It is for instance most unlikely that a good renal emptying is associated with a significant obstruction. The contrary is not true and many definitely non-obstructed systems may be associated with a poor drainage, even after furosemide and micturition, simply because of an important residual dilatation.

5. Radionuclide cystography

5.1. Direct radionuclide cystography (DRC)

5.1.1. Procedure

The procedure is comparable to the X-ray micturat-
ing cystourethrography (MCUG). A tracer (generally Tc-99m colloid) is instilled in the bladder through an indwelling catheter and the entire filling phase and voiding phase are recorded. An example is given in Fig. 5.

The technical details can be found in a recent guideline [15].

5.1.2. Advantages

– Favourable dosimetry compared to MCUG.
– Complete recording of filling and voiding phases available, thus providing a higher sensitivity for reflux detection than with MCUG [16,17].
– Applicable at any age.

5.1.3. Disadvantages

– The invasive character of placing an indwelling catheter.
– Poor resolution not allowing to demonstrate any morphological changes such as urethral valves, duplicated ureters, ureterocoele, ... best visualized on MCUG.
– Grading of reflux is not possible with DRC. One can however show that reflux reaches the kidney (at least reflux grade II) and that the reflux is intense or not, intermittent or not, visible during the filling phase or only during the micturition phase (active reflux).

5.2. Indirect radionuclide cystography (IRC)

5.2.1. Procedure and tracers

At the end of the renogram, the tracer has generally left the kidneys and is filling the bladder. The child who wishes to void can then be asked to void in front of the gamma camera, thus allowing the visualization of an active reflux, as represented in Fig. 6.

It is recommended to use a tracer with high extraction rate such as Tc-99m MAG3. Unsatisfactory results are obtained with Tc-99m DTPA, because of the still high renal activity.

The technical details of the procedure are fully explained in the guideline produced by the Paediatric Task Group of the European Association of Nuclear Medicine [18].

5.2.2. Advantages

– No indwelling catheter.
– Since IRC is a complement to the renogram, the functional parameters of the renogram (DRF and drainage) can be obtained as well.

5.2.3. Disadvantages

– Collaboration of the patient is necessary. Therefore, the technique is generally not used in children below 3 years of age.
– Interpretation of images may be more difficult than with DRC, since renal and ureteral activity may be present in the absence of reflux.
– Bladder filling is incomplete, resulting in lower sensitivity for reflux compared with DRC [19].

5.3. Proposed strategy

X-ray MCUG provides morphological information and, for that reason, will be required by many clinicians as a first approach.

Control cystography, during the medical or surgical follow up of a known reflux, should be performed in the nuclear medicine department. In children below 3 years of age, DRC should be used. In older children, IRC may be used instead, owing to its non-invasive character. However, if the result is negative, direct cystography is probably recommended because of its higher sensitivity.

References


