GUIDELINES FOR GLOMERULAR FILTRATION RATE DETERMINATION IN CHILDREN

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I Purpose

The purpose of this guideline is to offer to the nuclear medicine team a framework, which could prove helpful in daily practice. This guideline contains information related to the procedure and indications of measurement of glomerular filtration rate using blood samples in children.

The present document is inspired by the report of the Radionuclides in Nephrourology Committee on renal clearance [(1)], but contains information more specifically adapted to the European practice e.g. the choice of tracer.

This guideline summarises the views of the Paediatric Committee of the European Association of Nuclear medicine. It should be taken in the context of "good practice" of nuclear medicine and local regulation.

II Background information and definitions

Renal clearance of a substance can occur by two processes: glomerular filtration or tubular secretion. Of these processes, glomerular filtration rate (GFR) is probably the most representative parameter of renal function. It is relatively constant under standard conditions, and, as opposed to tubular secretion, is independent of the urine flow. This guideline is exclusively devoted to the determination of GFR.

The passive process of glomerular filtration can be quantified by measuring the clearance rate of a substance from the plasma, provided the following restrictions apply:

1. The substance must be freely filtrated through the glomerular membrane.
2. It must not undergo renal tubular secretion or reabsorption.
3. It must not bind to plasma proteins.
4. It must not interfere with renal function.
5. It must not be excreted through an extrarenal route.
6. It must be metabolically inert, neither binding to, nor being metabolised by other tissues.

The above criteria must be met when the GFR is calculated from the disappearance of the substance from the plasma (often called total plasma clearance), since this method contains the inherent assumption that plasma disappearance occurs exclusively via the kidneys. When urine collection is combined with plasma sampling (often called renal plasma clearance), the last two criteria may be relaxed, since renal excretion is measured directly.

GFR can be indirectly assessed from the plasma creatinine concentration. The measurement of plasma creatinine is easy, but this parameter is insensitive to moderate changes of GFR in that increases above reference range only occur when renal function is reduced by approximately 50 %. Several algorithms for assessing GFR have been published, all based on modifications of plasma creatinine by means of biometric parameters [(2-5)]. However, the individual errors are considerable and the standard error of the estimate may be as high as

50ml/min [6]. Moreover, the use of these methods in patients suffering from renal failure does not allow estimation of the effect of dietary protein restriction.

The direct assessment of GFR with inulin clearance, using the constant infusion technique and plasma and urine samples, constitutes the reference method for the measurement of GFR. This approach, rather complex and invasive, is not used in clinical routine. Endogenous creatinine clearance is generally considered as a good approximation in adults; in children, however, the correlation with inulin clearance is only fair, even in strictly controlled conditions [2]. Accurate measurement of GFR can be obtained by means of radioactive tracers such as ^{99m}Tc-DTPA and ^{51}Cr-EDTA [7,8]. Several gamma camera methods have been proposed but, at the present time, there is a consensus only on the determination of relative clearance [9]. The most accurate method for evaluation of absolute GFR is based on the plasma disappearance curve after single bolus injection of a glomerular tracer. The clearance of such a substance is given by the injected dose divided by the area under the curve. The area is best represented by a bi-exponential model [10]. This method, which is presently considered as a gold standard, is however infrequently used in children, because of the difficulties related to multiple blood sampling, particularly in infants. In a recent consensus [1], two accurate simplified methods have been proposed for clinical routine in children:

The "slope-intercept method"

This method is based on the determination of only the late exponential by means of at least two blood samples around 2 and 4 hours after intravenous injection of the tracer [11-13]. The fact of neglecting the early exponential introduces a systematic overestimation of the clearance that can be corrected using various published algorithms [12,13]. Several papers have underlined the accuracy of the slope-intercept method compared to the multiple blood sampling, for clearance values as low as 10ml/min [12-14]. Some investigators consider that a better determination of the slope can be obtained by using more blood samples within the 2-4-hr time interval. However, it has been shown [15] that no significant benefit is gained by adding a third intermediate blood sample. Late blood samples (5 to 24-hr) have been advocated in case of renal failure (patients with renal clearance below 10-15ml/min).

The "distribution volume" method

This method is based on a single blood sample taken at 2 hours [16]. The main advantage is the unique blood sample needed. This method is valid for children of any age and the results are identical to those of the slope-intercept method, but this approach is not valid in patients with poor renal function (GFR<30 ml/min/1.73m^2).

III Common Indications

Indications

A. Evaluation and follow up of renal function in chronic glomerulopathies such as hemolytic uremic syndrome and diabetes mellitus.

B. Evaluation and follow up of renal side effects of chemotherapy or nephrotoxic drugs such as cyclosporin and antibiotics.

C. Estimation of the single kidney GFR, in conditions such as unilateral or bilateral hydronephrosis, urinary tract infections with or without associated vesico-ureteral reflux, small kidney, single kidney, duplex kidney, urethral valves, pre-and postoperative follow up. Such an estimate requires a concomitant gamma camera relative uptake determination (see guidelines renography).

D. GFR determination can be considered each time renal impairment is suspected, even while plasma creatinine is in the normal range.

Contraindications

There are no contraindications.

IV Procedure

A. Information about previous examinations relevant to this procedure

- In case of significant oedema, the method cannot be used, since the plasma disappearance of the tracer will be influenced by the diffusion into an expanded extra-cellular volume. Clearance determination based on plasma and urine samples would be more adequate in that case.

- Plasma creatinine should be available since the choice between one or two blood sample technique depends on the level of renal function: plasma creatinine levels in excess of 124µmol/l probably indicates that two blood sample technique is more appropriate (see below).

B. Patient preparation

B.1 Information with appointment letter:

A written information about the procedure should be provided to the parents, best before the day of the examination.

B.2 Prior to injection:

Anaesthetic cream: is optional; if used, it should be applied at least 60 minutes before the injection.

Hydration: The patient should be adequately hydrated: an additional bottle one hour before tracer injection in babies; 250-500ml additional fluid (water, orange juice...) in older children.

It is to be noted that GFR, contrarily to tubular secretion, is not influenced by slight variations in the degree of hydration, due to autoregulation mechanisms. However, it could be wise to recommend a steady intake over the duration of the study.

Protein load may increase GFR and it is recommended to avoid protein enriched meals before GFR measurement.

Sedation: No sedation is needed.

C. Precautions

Nil.

D. Radiopharmaceutical

D.1 Radionuclide

- Chromium-51 (^{51}Cr) or
- Technetium-99m (^{99m}Tc).

D.2 Pharmaceutical

- Ethylene diamine tetraacetic acid (EDTA) or
- Diethylene triamine pentaacetic acid (DTPA)

^{51}Cr-EDTA is probably the best tracer for evaluation of GFR, related to the tight binding of Chromium to EDTA. ^{99m}Tc-DTPA is a valuable alternative, providing that the purity is guaranteed. The same algorithms for calculation of GFR can be used for both tracers [17].

D.3 Dose Schedule

- ^{51}Cr-EDTA
  Minimal dose: 0.074 MBq / kg.
  Maximal dose: 3.7 MBq.

- ^{99m}Tc-DTPA
  The administered dose is scaled on a body surface basis [18]. Maximal dose: 37 MBq. If DTPA gamma camera images and relative function is required, the doses should be higher (see guidelines on renography).

D.4 Measurement of dose, standard, blood samples; injection of tracer

4.1. Equipment quality control

Quality control of the equipment is essential: (J. Quality control).

4.2. Syringe preparation

Prepare two identical syringes, one with the dose to be injected and one with an aliquot of the dose (”standard”). The volume should be at least one ml and comparable in both syringes (add 0.9% saline if necessary).

4.3. Measurement of the dose and the standard

Either of the following methods can be used:

4.3.1. External counter or gamma camera.

Measure both syringes in exactly the same conditions, including the distance to the detector. Avoid placing the syringes too close to the detector or surface of the collimator. Background should be subtracted.

4.3.2. Weighing both syringes.

This should be done on a high precision balance. The method is more precise than the external counter/gamma camera technique. The empty syringe must however not be rinsed (see 4.5.2).

4.4. Injection technique

The dose should be injected strictly intravenously; any extravasation will invalidate the result.

It is recommended to use different sites for injection and blood sampling. For that purpose, a fine butterfly needle (calibre 27) is adequate, connected to a three-way stopcock. To the first port, attach a syringe containing 0.9% saline (5 to 10 ml) in order to test the position of the needle into the vein and to the second port, attach the syringe containing the tracer. Inject the tracer and rinse the syringe two or three times using the saline of the first syringe. Note the exact time of intravenous injection: radiocontrolled clocks may be useful. If an imaging study with DMSA or MAG3 is combined with GFR determination using ^{51}Cr-EDTA, then it might be better to inject EDTA first. Avoid the use of long plastic tubing such as those placed in the clinical departments for intravenous perfusion.

Some investigators will give preference to the placing of a Venflon needle with a valve, allowing both the tracer injection and repeated blood sampling with only one venepuncture. To eliminate the risk for contamination of the blood samples, the tracer injection should then be done through the port with the valve, followed by 5-10 ml of saline through the same port and another 5-10 ml through the other port. The blood samples are drawn at appropriate times from the back port of the Venflon fitted with a 3-way stop-cock after discarding 3-5 ml "waste" blood.

4.5. Measurement of the empty syringe

This should be done using the same method used to measure the dose and the standard, and in the same conditions:

4.5.1. External counter

Measure the empty syringe and note the exact time of counting. Ideally, if the tracer has been adequately rinsed during intravenous injection, no remaining activity should be found in the empty syringe.

If DTPA has been used, it is necessary to correct this measurement for Technetium-99m decay, taking the time of measurement of the dose and standard as initial time point.

4.5.2. Weighing the empty syringe

This method demands that the empty syringe have not been rinsed at the time of injection.

4.6. Blood sampling

If the "slope-intercept" method is used, two blood samples should be taken, ideally at 2 and 4 hours. It is however not necessary to have these blood samples taken exactly at 2 and 4 hours. The first blood sample can be taken as early as 90 minutes, whereas the second blood sample can be taken much later than 4 hours. The interval between the two blood samples should be at least 2 hours and probably longer when a low clearance value is anticipated [15]. The exact moment of blood sampling should be noted. Since the procedure may take one minute or even more, it is the midpoint of the blood sampling which should be taken.

If the one-sample technique is used [16], the blood sample should necessarily be taken between 110 and 130minutes after intravenous injection.

The blood should be injected into a perfectly dry tube, with or without dried heparin on the surface of the tube. Clotting however is unimportant and will not affect the measurements.

After centrifugation, 1.0ml plasma should be taken precisely and transferred into a counting vial. If enough plasma remains, a second 1.0ml sample can be taken.

4.7. Conversion factor

The injected dose, contrarily to the plasma sample, cannot be measured in a well counter. In order to make the injected dose measurement on the camera comparable to the plasma activity measurement in the well counter, a conversion factor must be introduced. For that purpose, the standard is measured in the same conditions as the dose (see D.4.3) and, after dilution, in the same conditions as the blood sample (well counter). The ratio between these two measurements constitutes the conversion factor.

In order to measure the standard in a well counter, it has to be diluted: transfer the syringe contents (standard) into a volumetric flask (e.g. 500ml) and rinse the syringe several times so that all the remaining activity from the syringe is placed in the flask. Note that if the weighing method is used, the syringe must not be rinsed. Fill the volumetric flask with water to the 500-ml level and mix the solution thoroughly. Pipette twice 1.0ml of this new solution into counting vials. Substantial variations in counts between standard samples indicate an error, either in pipetting or in the homogeneity of the solution. New samples from the dilution of the standard should then be prepared.

The dose can now be calculated as if it were measured in a well counter:

$$\text{Dose} = \frac{(D - R) \times ADS \times DS}{AS}$$

where, if the external detector technique is used,

AS = activity of the standard measured on the external detector.

D = dose, measured on the external detector before intravenous injection.

R = residue of the dose after intravenous injection, measured on the external detector.

ADS = activity of 1 ml of the dilution of the standard.

DS = dilution of the standard (e.g. 500).

If the weighing technique is used,

AS is now the weight of the aliquot used to make the standard;

D and R are the weight of the dose respectively before and after injection.

4. 8. Well counter

After selection of the adequate energy peak and window, both the blood samples and the standard are measured in a well counter. This should be done the day of the examination if ^{99m}Tc-DTPA has been used. If a Tc-99m compound such as MAG3 or DMSA has been injected together with Cr-51 EDTA, it is better to wait 48-hours before counting the ^{51}Cr activity, in order to avoid the interference of ^{99m}Tc activity.

For quality control reasons, each plasma sample and standard vial should be counted twice. It is recommended, if possible, to use duplicate plasma samples for each patient and those 2 aliquots of the standard should also be measured. A background activity should be measured in the beginning and at the end of the counting. Plasma samples from several patients can be counted using the same standard.

Again, it is important to correct for ^{99m}Tc decay, considering the delay of time between the successive measurements in the well counter.

Counting times, particularly for the ^{51}Cr activity, should be long enough to avoid errors related to statistical errors (the statistical error is 1% for 10 Kcounts collected).

D.5 Radiation burden

For ^{51}Cr-EDTA, the effective dose (ED) is approximately 0.011mSv / examination regardless of the age of the child, providing that the dose is adapted according to body weight [19].

In case of poor renal function (10 ml/min/1.73m^2), the radiation dose is twice as high [20].

For ^{99m}Tc-DTPA, ED is approximately 0.1mSv/examination [21]

E. Image acquisition

Not pertinent.

F. Interventions

Not pertinent.

G. Processing

G.1 Two-sample method (slope -intercept method)

In this simplified system, one is neglecting the early exponential.

The clearance can then be expressed as: $Cl_1 = D / A$.

Where, D is the injected dose (see D.4.7 and D.4.8) and A is the estimated area under the plasma curve.

The area is obtained from the exponential fitting of the late plasma sample activities:

Area = Y_0 / b.

Where, Y_0 is the intercept of this late exponential at time 0 and b is the slope or rate constant of this exponential.

The same equation can be expressed differently, using only the plasma sample activities and the sample times:

$$Cl_1 = \frac{D \times \ln (P_1/P_2)}{T_2 - T_1} \exp \frac{(T_1 \ln P_2) - (T_2 \ln P_1)}{T_2 - T_1}$$

Where, D = administered activity (cpm);

P_1 = activity at T_1;

P_2 = activity at T_2;

P_1 and P_2 are in counts / min/ml.

Cl_1 is a preliminary estimate of GFR and should first be corrected for body surface.

Body surface can be estimated on the basis of the child's height and weight, using Haycock's equation [22] :

$Cl_2 = Cl_1$ x 1.73 / body surface area.

Then, because of the overestimation of the slope-intercept method related to the fact that the first exponential has been neglected, one should introduce a correction factor, using one of the following methods:

- The Chantler's method [12] is a linear correction:

$$GFR = 0.87 \times Cl_2,$$

where

GFR is in ml /min /1.73 m^2 (corrected for the first exponential and body surface area).

This type of correction is adequate for normal and high clearance levels but underestimates the low clearance values.

- The Bröchner Mortensen's method [11] implies a quadratic correction which theoretically takes into account the fact that for low clearance values the first exponential is negligible, while it is important for high clearance values:

$$GFR = 1.01 \times Cl_2 - 0.0017 \times Cl_2^{\,2}$$

where,

GFR is in ml /min / 1.73 m^2 (corrected for body surface area and for neglecting the early exponential).

The correction in the high range of clearance is however exaggerated, giving rise to an inadequate compression of the values and a possible underestimation of the clearance in case of hyperfiltration.

G.2 One sample method (16)

$$Cl\ (ml / min) = (2.602 \times V_{120}) - 0.273$$

where,

V_{120} is the so-called "virtual distribution volume" at 120-min post-injection, this volume (in litres) being the injected dose divided by the plasma concentration at 120-minutes.

Since blood sampling does not occur exactly at 120 minutes , a small correction factor is introduced, which is however valid only if blood sampling occurs in the range of 110-130 min post-injection:

$$P_{120} = P_{(t)} \times e^{0.008\,(t\,-120)}$$

where, t is the blood sampling time (110-130 minutes) and $P_{(t)}$ is the plasma concentration at that time.

The final GFR result has to be corrected for body surface area.

H. Hard copy output

Body surface corrected and non-corrected clearance should be given as well as the distribution volume in % of weight. This last parameter, only available if the slope intercept method is used, can be helpful as a quality control: it is unusual that the distribution volume is less than 15% or more than 40 %.

I. Interpretation/Reporting/Pitfalls

I.1 Normal values

Estimated normal values, corrected for body surface, have been published [23]. The clearance level, uncorrected for body surface, increases progressively from birth up to adulthood. The body surface area corrected clearance increases from birth to more or less 2 years and then remains constant into adulthood. The lower levels are probably correct but the upper levels are overestimated since many of these "normal" patients have had recent urinary tract infection and might therefore have developed hyperfiltration [24].

I.2 Pitfalls

Below 10 ml / min /1.73 m^2, plasma clearance method becomes inaccurate.

Below more or less 30 ml / min/1.73 m^2, the one-blood sample method cannot be used.

Children below one month have a low clearance value due to renal immaturity, even if corrected for body surface. Since the absolute error in the clearance estimate, expressed in ml / min, is comparable to what is observed in older children, the relative error, expressed in % of the clearance value, is large.

J. Quality control

Check the performances of the gamma camera (count rate, homogeneity), the well counter, the balance.

Check the purity of the DTPA preparation (regular chromatography).

Check the absence of significant oscillations between successive measurements of the same sample or between two aliquots issued from the same dilution (standard) or from the same plasma sample.

Check the linearity of the external counter and the well counter

Check the distribution volume: this volume should be between 15 and 40 % of body weight (unpublished data, Sixt).

V Issues requiring further clarification

1. Reappraisal of normal values in children.
2. Reappraisal of day to day variation in patients without progressive disease.

VI Concise Bibliography

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