European Journal of
Nuclear
Medicine

Original article

# Estimation of normal chromium-51 ethylene diamine tetra-acetic acid clearance in children

A. Piepsz[1,2], H. Pintelon[1], H.R. Ham[2]

[1] Department of Radioisotopes, Academic Hospital, VUB, Brussels, Belgium
[2] Department of Radioisotopes, Hôpital Saint-Pierre, Brussels, Belgium

Received 27 May and in revised form 2 August 1993

**Abstract.** In order to estimate the normal range of chromium-51 ethylene diamine tetra-acetic acid (EDTA) clearance in children, we selected a series of 256 patients with past or present urinary tract infection who showed, at the time of the clearance determination, normal technetium-99m dimercaptosuccinic acid (DMSA) scintigraphy and normal left to right DMSA relative uptake. The clearance was calculated by means of either the simplified second exponential method or the 120-min single blood sample; Chantler's correction was used in order to correct for having neglected the first exponential. There was a progressive increase in clearance from the first weeks of life (mean value around 1 month: 55 ml/min/1.73 $m^2$), with a plateau at around 18 months. Between 2 and 17 years of age, the clearance values remained constant, with a mean value of 114 ml/min/1.73 $m^2$ (SD: 24 ml/min); this is similar to the level described for inulin clearance. No significant differences were observed between boys and girls, or between clearance values calculated with one or with two blood samples. Taking into account the hour of intravenous injection of the tracer, we did not observe any influence of the lunchtime meal on the distribution of the $^{51}$Cr-EDTA clearance values.

*Key words:* Glomerular filtration – Chromium-51 ethylene diamine tetra-acetic acid – Children – Normal values

**Eur J Nucl Med (1994) 21:12–16**

## Introduction

Glomerular filtration rate (GFR) remains the most important functional parameter in paediatric nephrology. Although inulin clearance measured during constant infusion is considered the reference method, it is not suited for daily clinical use; the results of correlations between 24-h creatinine and inulin clearance have not been wholly satisfactory, some reports having shown overestimation of creatinine clearance for low clearance values and even for normal clearance values [1, 2]. Simplified methods based on plasma creatinine and biometric parameters have not been found to be an ideal alternative to inulin clearance [3].

Chromium-51 ethylene diamine tetra-acetic (EDTA) clearance using biexponential or uniexponential analysis is considered a good reflection of GFR [4, 5] and is widely used in adults and children for estimation of overall GFR. However, to the best of our knowledge, normal values have never been published in adults and children: $^{51}$Cr-EDTA clearance is found to be closely correlated with inulin clearance [4, 5] and the normal range is generally estimated from the normal range of inulin clearance.

The aim of this paper was to try to estimate retrospectively the normal values of $^{51}$Cr-EDTA clearance in children, on the basis of a clinical series.

*Correspondence to:* A. Piepsz, AZ VUB, Department of Radioisotopes, Laarbeeklaan 101, B-1090 Brussels, Belgium

## Materials and methods

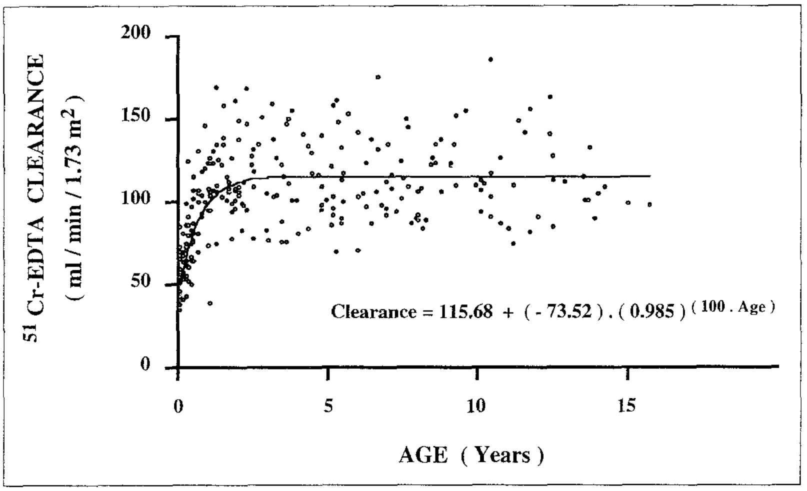
*Criteria of selection.* Patients were retrospectively selected from a data base including all children who underwent combined technetium-99m dimercaptosuccinic acid (DMSA) scintigraphy and $^{51}$Cr-EDTA clearance because of urinary tract infection. The examination was performed either within the first 3 days after the diagnosis of acute infection or as an additional examination in asymptomatic patients with a history of recurrent urinary tract infection. The children were normally hydrated at the time of examination and blood urea and creatinine were always normal. Only those patients having strictly normal DMSA images and a relative uptake percentage for each kidney of between 45% and 55% were included in the present study.

*$^{99m}$Tc-DMSA scintigraphy.* $^{99m}$Tc-DMSA scintigraphy was performed 2–5 h after injection of the tracer, at a dose scaled on a body surface area basis to an adult dose of 185 MBq. One posterior and two posterior oblique views were available. Zoom facilities and sometimes pinhole views were used in small children.

**Table 1.** Overall results of $^{51}$Cr-EDTA clearance (ml/min/1.73 m$^2$)

| | Age | No. | Age | | Clearance | | |
|---|---|---|---|---|---|---|---|
| | | | Mean | Range | Mean | SD | Range |
| All patients | | 256 | 4.2 | 0.08–15.80 | 102.9 | 29.9 | 35–186 |
| | <2 years | 114 | 0.7 | 0.08–1.90 | 87.7 | 30.0 | 35–169 |
| | ≥2 years | 142 | 6.8 | 2.00–15.80 | 114.2 | 24.3 | 69–186 |
| 2 blood samples | <2 years | 49 | 0.8 | 0.08–1.91 | 87.4 | 29.6 | 35–161 |
| 1 blood sample | <2 years | 65 | 0.7 | 0.08–1.91 | 88.0 | 30.6 | 38–169 |
| 2 blood samples | ≥2 years | 76 | 7.3 | 2.00–15.00 | 113.8 | 23.3 | 70–186 |
| 1 blood sample | ≥2 years | 66 | 6.5 | 2.00–15.80 | 114.7 | 25.8 | 69–176 |
| Males | <2 years | 72 | 0.6 | 0.08–1.90 | 81.4 | 28.3 | 35–161 |
| Females | <2 years | 42 | 0.9 | 0.08–1.80 | 98.6 | 30.3 | 43–169 |
| Males | ≥2 years | 37 | 6.5 | 2.00–13.80 | 116.1 | 22.2 | 75–158 |
| Females | ≥2 years | 105 | 6.9 | 2.00–15.80 | 113.5 | 25.1 | 69–186 |

SD, Standard deviation



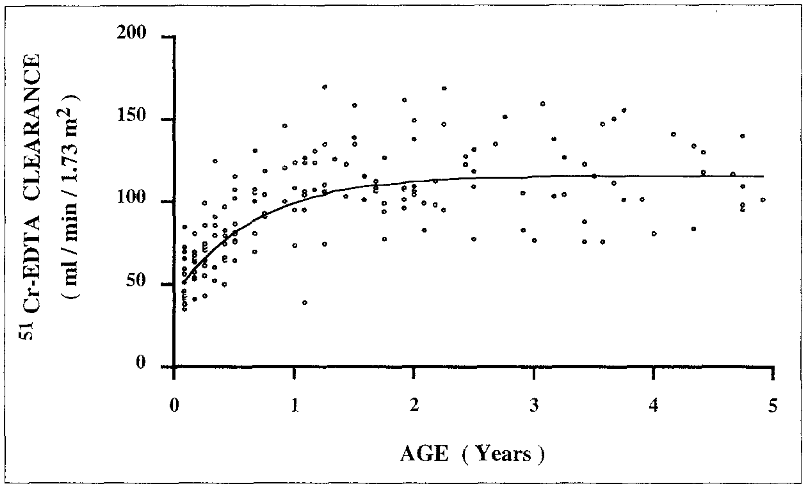




**Fig. 1.** Plot of the $^{51}$Cr-EDTA clearance values as a function of age. *Upper panel*: Clearance values between 3 weeks and 16 years; the equation of the non-linear fit is represented. *Lower panel*: In order to illustrate the progressive increase in clearance with age, the values between 3 weeks and 5 years are shown

The normality criteria included the absence of any localized hypoactive area (except the normal hypoactive area at the site of the calyces) as well as of any deformity of the kidney outlines (except the normal spleen impression). The left to right ratio was calculated from regions of interest drawn around both kidneys and after subtraction of a small amount of background activity from the supra- and subrenal areas.

*$^{51}$Cr-EDTA clearance.* The injections of $^{51}$Cr-EDTA, according to body surface area and on the basis of an adult dose of 1.85

**Table 2.** Values of $^{51}Cr$-EDTA clearance for various age groups

| Age (years) | No. | $^{51}Cr$-EDTA clearance (ml/min/1.73 m$^2$) | | |
|---|---|---|---|---|
| | | Mean | SD | CV (%) |
| <0.10 | 18 | 54.6 | 14.1 | 25.8 |
| 0.10–0.30 | 18 | 65.2 | 14.4 | 22.1 |
| 0.31–0.66 | 22 | 81.8 | 19.2 | 23.5 |
| 0.67–1.00 | 17 | 103.8 | 20.1 | 19.4 |
| 1.00–1.50 | 20 | 116.6 | 28.3 | 24.2 |
| 1.51–2.00 | 19 | 111.5 | 19.8 | 17.8 |
| >2.00 | 142 | 113.9 | 24.4 | 21.5 |

SD, Standard deviation; CV, coefficient of variation

MBq, were administered between 8 a.m. and 3 p.m. and no particular precautions were taken as far as the meals were concerned: patients injected at 1 p.m. often had a lunch including meat at around 11.30 a.m. Moreover, the children were allowed to move freely between the time of the injection and the time of blood sampling

Until November 1990, we used the technique of the second exponential determined by means of two blood samples. After that period, only one blood sample was taken at 2 h and the clearance was derived from 2-h "distribution volume".

*Two-blood-sample technique.* Blood samples were taken at 2 and 4 h after intravenous injection of the tracer [4, 5]. The injected dose, an aliquot of the dose and the residual activity in the syringe which contained the injected dose were counted in standard conditions by means of an external detector. A dilution of the aliquot as well as the plasma samples were counted in a well counter. A small specially designed computer program allowed rapid determination of the plasma exponential slope at between 2 and 4 h; the extrapolation of this curve at time zero gave the "distribution voulume" of the tracer and the clearance was obtained by multiplying the distribution volume by the slope of the second exponential. Since we neglected the first exponential, the values were overestimated and we therefore applied Chantler's constant 0.87 correction factor to the calculated clearance [6]. All the values were corrected for body surface.

*One-blood-sample technique.* One blood sample was taken between 115 and 125 min after injection of the tracer, and blood, injected dose, aliquot of the dose and residual activity were measured as described in the two-blood-sample technique. A "distribution volume" was calculated by dividing the injected dose by the plasma concentration at 2 h and was converted in terms of clearance using a regression equation previously developed [7]. Clearance values were then corrected for body surface area.

*Patients.* Using the applied criteria, 256 patients were selected. Clearance was calculated by means of two blood samples in 125 patients, and by means of one blood sample in 131 patients. 114 patients were below 2 years of age (72 boys, 42 girls); 142 were above 2 years of age (37 boys, 105 girls).

## Results

The clearance results were divided taking into account the type of $^{51}Cr$-EDTA technique used (one or two blood samples), the age (below or above 2 years) and the sex. Table 1 summarizes the results in these subgroups. Clearance results with one or two blood samples were comparable, above as well as below 2 years of age. Considering the entire group of 256 patients, there was a progressive increase in clearance from the first weeks of life (the lowest age was 21 days and the mean clearance value below 1 month of age was 54.6 ml/min/1.73 m$^2$), reaching a plateau at around 18 months. Between 18 and 24 months, the clearance values were not different from those observed later. Between 2 and 17 years

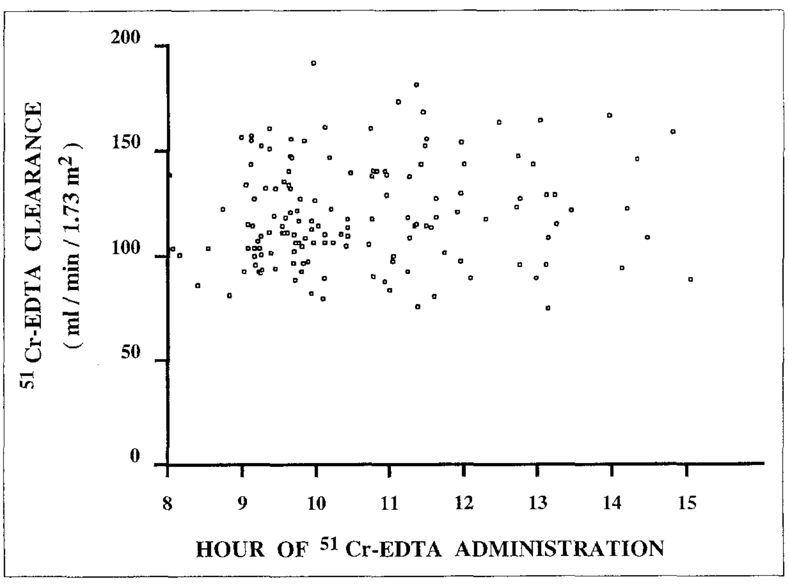



**Fig. 2.** Plot of the $^{51}Cr$-EDTA clearance values against the hour of administration of the tracer

of age, the clearance values remained constant, with a mean value of 113.9 ml/1.73 $m^2$ (SD: 24.4 ml/min). These data are illustrated in Fig. 1, in which a non-linear fit (modified geometric function) is plotted, describing the relationship between clearance and age.

In the group above 2 years of age, the histograms of ages were similar in boys and girls; the mean clearance value was 116.1 ml/min in boys (SD: 22.2) and 113.1 ml/min in girls (SD: 25.1). Below 2 years of age, the mean clearance was 81.4 ml/min in boys (SD: 28.3) and 98.6 ml/ml in girls (SD: 30.3), but the mean age was also slightly lower in boys (mean age: 0.60 years) than in girls (mean age: 0.90 years). The mean values for different age groups are shown in Table 2.

In order to evaluate the potential influence of the lunchtime meal, we have examined the relation between the clearance value in children older than 2 years and the hour at which the tracer was injected (Fig.2). No influence of the hour of injection on the value of the clearance could be detected.

## Discussion

Despite the fact that $^{51}$Cr-EDTA clearance has been validated as a method for estimating GFR for more than 20 years [4], values obtained from a series of normal volunteers are not available in the literature. Several authors [4, 5] have shown that $^{51}$Cr-EDTA clearance is closely correlated to standard chemical clearances, like inulin or creatinine clearance and, therefore, normal $^{51}$Cr-EDTA clearance values are usually derived from the normal chemical data. In children, the problem is even more difficult since GFR, even after correction for body surface area, inreases with age during the first years of life [8].

For ethical reasons, true normal values cannot be determined in children. We therefore decided to estimate the normal values from a population of patients having a low probability of renal impairment. DMSA scintigraphy is at present considered to be the most sensitive test for the detection of acute or chronic renal abnormalities, although the sensitivity is certainly not perfect [9, 10]. Except in children below 3 months of age, in whom the quality of the scintigrams is not always ideal, Jakobsson et al. [11, 12] consider that a normal DMSA scintigram practically excludes the diagnosis of upper urinary tract infection. Studying inulin and para-aminohippuric acid clearance in children with recurrent pyelonephritis, Berg [13, 14] showed that the clearance rate was related to the grade of morphological impairment; when both kidneys were normal, the clearance values were still slightly lower than in the normal control group. However, the normality of the kidneys was estimated on the basis of intravenous urography which, even in the opinion of the author [11], is less sensitive than DMSA scintigraphy. We therefore consider that our population of patients included mainly acute lower urinary tract infections, or asymptomatic patients with a history of previous lower urinary tract infection. We do not, however, exclude the possibility that some of our patients (and particularly some infants) had acute pyelonephritis not detected by scintigraphy. In fact, even if acute pyelonephritis were present, it would not necessarily mean that a decrease in GFR would have to be postulated in these cases. Berg [14] has shown that children presenting their first episode of pyelonephritis after the age of 3 years had normal inulin clearance.

While some of the low values in the large range observed in our population (75 ml–170 ml/min/1.73 $m^2$) may have been due to the selection of patients, errors related to the technique of $^{51}$Cr-EDTA clearance itself are more likely to have been responsible for the wide variation. Such errors are partial paravenous injection, errors in sampling, errors in time counting and errors in reporting the exact time of blood sampling. It is to be underlined that most of these errors cannot be detected afterwards, particularly with the one-blood-sample technique; two blood samples, allowing the calculation of a volume of distribution, at least permit one to check that the distribution volume is not completely outside of the usual range. In the present study, we found, after 2 years of age, a mean distribution volume of 30.1% of body weight (SD: 6.5%). Further studies are needed to evaluate the reproducibility of $^{51}$Cr-EDTA clearance performed several times in the same patient: Are values as low as 75 ml/min due to accidental technical failures or do they indeed represent the lower range of normal values?

Finally, it is noteworthy that a similar wide normal variation has also been described for chemical clearance. Smith [15], reviewing the series published on inulin clearance, noted values as low as 70 ml/min/1.73 $m^2$ and as high as 176 ml/min. It is therefore possible that the values reported in the present work indeed correspond to a wide normal spectrum.

Even after correction for body surface area, we found a progressive increase in clearance with age, the adult level being reached at somewhere between 15 and 24 months. This is illustrated by the non-linear fit on the whole series of data presented in Fig. 1. This evolution is in agreement with that of inulin clearance in children [8], and similar maturation patterns have been described for other tracers like $^{99m}$Tc-diethylene triamine pentaacetic acid [16], $^{197}HgCl_2$ [17] and $^{99m}$Tc-DMSA [18].

It is important to underline that, from a theoretical point of view, neglecting the first exponential of the plasma disappearance curve of $^{51}$Cr-EDTA produces an overestimation of the clearance. Chantler and Barratt [6] have introduced a correction factor based on a linear regression between biexponential and uniexponential clearance, in children with different levels of clearance. This is the method of correction which has been used in the present work.

Böchner-Mortensen et al. [19] observed that the influence of the first exponential is not equal whatever the level of clearance: for low clearance values, the percentage of the clearance value which should be subtracted is less important than for high clearance values. For this reason, and on the basis of a series of clearance values determined in children by means of both bi- and uniexponential analysis, they calculated a correction factor dependent on the clearance level: clearance corrected=1.01 (clearance non-corrected) −0.0017 (clearance non-corrected)$^2$ ml/min/1.73 m$^2$. It should be noted, however, that the fit has been established on the basis of clearance values lower than 120 ml/min. Higher values were simply extrapolated from the fit. It is easy to show that, using this algorithm, the highest clearance value which can be obtained mathematically is 150 ml. In other words, this correction introduces an exaggerated compression of the values at the upper range of clearance. Below 120 ml/min, the results obtained by means of a constant correction are not very different from those obtained by means of a more complicated equation. This was already pointed out by Chantler and Barratt [6].

With our $^{51}$Cr-EDTA clearance values, the use of the Bröchner-Mortensen correction instead of the Chantler correction would lower the mean clearance value from 114 to 105 ml/min/1.73 m$^2$ for children older than 2 years. Similarly, the standard deviation would be half as large, but this would be due only to the artificial effect of compression of the high clearance values.

In a recent work [20], it has been shown that, using a biexponential analysis of clearance as reference, the Bröchner-Mortensen correction gives more accurate results for the simplified uniexponential method than no correction at all. It is obvious from the inspection of these data, however, that this correction factor introduces an over-correction for high clearance values. A better approximation of the "true" clearance results could have been obtained by applying Chantler's algorithm on the non-corrected data.

In the present work, the absence of any difference between the one-blood-sample and the two-blood-sample clearance excludes a systematic bias related to the methodology. Previous work [7] has shown that the difference between these two methods for an individual patient does not exceed 3 ml/min (values not corrected for body surface area).

We have not found any difference between males and females. In adult patients, some series reported by Smith [15] revealed a higher clearance in males than in females; other series reported by the same author show similar ranges for both sexes.

In our routine practice, no particular attention is devoted to the meal preceding the injection of $^{51}$Cr-EDTA. Since patients having their injection after 12 a.m. were more likely to have received a lunch including protein (meat etc.), we analysed the distribution of the clearance values as a function of the hour of tracer injection: no obvious increase in clearance could be observed after 12 a.m.

## References


1. Dodge WF, Travis LB, Daeschner CW. Comparison of endogenous creatinine clearance with inulin clearance. *Am J Dis Child* 1967;113: 683–685
2. Kassirer JP. Clinical evaluation of kidney function- glomerular function. *N Engl J Med* 1971;285: 385–389
3. Guignard JP, Torrado A, Feldman H, Gautier E. Assessment of glomerular filtration rate in children. *Helv Paediatr Acta* 1980;35: 437–447
4. Chantler C, Garnett ES, Parsons V, Veall N. Glomerular filtration rate and measurement in man by the single injection method using $^{51}$Cr-EDTA. *Clin Sci* 1969;37: 169–180
5. Bröchner-Mortensen J. Routine methods and their reliability for assessment of glomerular filtration rate in adults. *Dan Med Bull* 1978;25: 181–202
6. Chantler C, Barrett TM. Estimation of glomerular filtration rate from plasma clearance of 51 chromium edetic acid. *Arch Dis Child* 1972;47: 613–617
7. Ham HR, Piepsz A. Estimation of glomerular filtration rate in infants and children using a simple plasma sample method. *J Nucl Med* 1991;32: 1294–1297
8. Barratt TM, Chantler C. Laboratory evaluation. In: Rubin MI, Barratt TM, eds. Paediatric nephrology. Baltimore: Williams and Wilkins;1986: 282–299
9. Stokland E, Hellström M, Jodal U, Lundgren P, Sixt R. DMSA scintigraphy in children with acute first time urinary tract infection. *Eur J Nucl Med* 1992;19: 629
10. Piepsz A, Tamminen-Möbius T. Correlation between scintigrphic lesions and renal scarring in intravenous urogram in children with normal relative uptake of DMSA and evaluation of normal kidney findings of DMS scan. In: Blaufox, Hollenberg, Raynaud, eds. Radionuclides in nephrology. Basel: Karger;1990: 147–155
11. Jakobsson B, Söderlundh S, Berg U. Diagnostic significance of $^{99m}$Tc-dimercaptosuccinic acid (DMSA) scintigraphy in urinary tract infection. *Arch Dis Child* 1992;67: 1338–1342
12. Jakobsson B, Nolstedt L, Svensson L, Söderlundh S, Berg U. $^{99m}$Tc-DMSA scan in the diagnosis of acute pyelonephritis in children: relation to clinical and radiological findings. *Pediatr Nephrol* 1992;6: 328–334
13. Berg UB. Renal dysfunction in recurrent urinary tract infections in childhood. *Pediatr Nephrol* 1989;3: 9–15
14. Berg UB. Long term follow up of renal morphology and function in children with recurrent pyelonephritis. *J Urol* 1992;148: 1715–1720
15. Smith HW. The kidney structure and function in health and disease. New York: Oxford University Press,1951
16. Piepsz A, Hall M, Ham HR, Verboven M, Collier F. Prospective management of neonates with pelviureteric junction stenosis. *Scand J Urol Nephrol* 1989;23: 31–36
17. Raynaud C. Valeurs normales de la fixation du Hg chez l'enfant âgé de moins de 4 ans. In: Raynaud C, ed. *La fixation rénale du mercure et du DMSA*. CEA;1976: 146–149
18. Gordon I, Evans K, Peters AM. The quantitation of $^{99m}$Tc-DMSA in paediatrics. *Nucl Med Commun* 1987;8: 661–670
19. Bröchner-Mortensen J, Haahr J, Christoffersen J. A simple method for accurate assessment of the glomerular filtration rate in children. *Scand J Clin Lab Invest* 1974;33: 139–143
20. Piciotto G, Cacace G, Cesana P, Mosso R, Ropolo R, De Filippi PG. Estimation of chromium-51 ethylene diamine tetraacetic acid plasma clearance: a comparative assessment of simplified techniques. *Eur J Nucl Med* 1992;19: 30–35