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ORIGINAL ARTICLE

Reassessment of a classical single injection ^{51}Cr-EDTA clearance method for determination of renal function in children and adults. Part II: Empirically determined relationships between total and one-pool clearance

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Background. The one-pool or slope-intercept technique is widely used when determining total ^{51}Cr-EDTA plasma clearance (Cl). The one-pool clearance (Cl_1), which always exceeds Cl, has mostly been corrected to Cl by multiplication by a constant factor=0.80, suggested by Chantler ($CH_{0.80}$), or by using a second-order polynomial originally proposed by Brøchner-Mortensen (BM) and later recommended by the British Nuclear Medicine Society (BM_{BNMS}). Theoretical considerations indicate that the CH correction gives a systematic overestimate of Cl, whereas the BM correction may underestimate Cl at high values. ***Objective***. To assess the accuracy of Cl as estimated from Cl_1 corrected either by $CH_{0.80}$ or by second-order polynomials. ***Material and methods***. Cl_{ref} was determined in 149 subjects (M/F/children: 71/46/32) from a complete plasma curve followed for 4–5 h after injection of ^{51}Cr-EDTA (range of Cl_{ref}: 8–183 mL/min/1.73 m^2). Cl_{est} was determined from Cl_1 subsequently corrected by $CH_{0.80}$ and four second-order polynomials. ***Results***. Using $CH_{0.80}$ correction, Cl_{est} underestimated Cl_{ref} (by a maximum of 20 %) at Cl_{ref} values less than about 100 mL/min/1.73 m^2 in children and 130 mL/min/1.73 m^2 in adults. At higher clearance levels, Cl_{ref} was increasingly overestimated. Taking the BM_{BNMS} correction as representative of second-order polynomials, Cl_{est} increasingly underestimated Cl_{ref} at high levels, the error being 10 % at a Cl_{ref} value of about 175 mL/min/1.73 m^2. **Conclusions.** We suggest that the tested correction equations are replaced by the given common correction equation based on the "true" relationship between Cl_1 and Cl thoroughly described in part I of this study.

Keywords: ^{51}Cr-EDTA; glomerular filtration rate; plasma clearance; renal function; slope-intercept technique

Introduction

The total plasma clearance of ^{51}Cr-EDTA (Cl) determined after i.v. bolus injection is widely used as a standard measure of renal function (GFR). The true Cl is determined as the ratio between the injected amount of tracer and the area under the entire plasma concentration curve, i.e. from the time of injection until all injected tracer substance has been excreted. To make the technique more convenient with the need for only a few blood samples, the so-called one-pool or slope-intercept technique [1,2] is nowadays a widely used simplified version. With this technique, a one-pool clearance (Cl_1) is determined as the ratio between the injected amount of activity and the area under the final monoexponential part of the plasma curve. Since this area is always lower than the area under the complete plasma curve, Cl_1 always exceeds Cl and a correction is needed. Hitherto, Cl_1 has mostly been corrected to Cl by a constant factor [1] as $Cl=\text{constant}\cdot Cl_1$, or using a second-order polynomial of the general form $Cl=a+b\cdot Cl_1+c\cdot Cl_1^2$ [2–4]. Some authors have compelled the intercept to be zero [2,3], but others have not [4]. For the most part, however, the resulting estimates of Cl have been indistinguishable [5].

According to the original Brøchner-Mortensen version in adults [2], the correction equation is used *without* preceding scaling of Cl_1 to a body surface area (BSA) of 1.73 m^2. However, the same equation is also used *with* preceding scaling of the one-pool clearance to 1.73 m^2, $Cl_{1,BSA}$ [5,6]. In the algorithm for children [7], and in the common correction equations for children and adults as recommended by the British Nuclear Medicine Society [8], $Cl_{1,BSA}$ is used as the independent variable.

In a recent study, Fleming [9] showed that the empirically determined relationship in adults between Cl and Cl_1 by Brøchner-Mortensen [2] increasingly underestimates Cl at high values, whereas the Chantler correction, using a constant factor [1], gives

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a systematic overestimate of *Cl*. In part I of our study [10] we derived analytically correct relationships between *Cl* and Cl_1 and between Cl_{BSA} and $Cl_{1,BSA}$. Using these analytical relationships and *Cl* determined from the complete plasma concentration curve in a great number of subjects comprising children and adults, we aim in the present study to assess the presumed errors of the above-mentioned empirically determined correction equations, three of which are used in children [1,7,8] and four in adults [1,2,8].

Material and methods

Subjects investigated

The present study comprised a total of 149 subjects (M/F/children=71/46/32) who all had *Cl* determined from a complete plasma concentration curve after i.v. bolus injection of ^{51}Cr-EDTA. None had oedemata, and they were chosen from four previously published studies. *Study 1* [11]: Sixty-nine patients and 17 normal subjects. The patients had known or suspected nephro-urological disorders and were referred to routine investigation of the renal function. *Study 2* [12]: Sixteen type 1 diabetics investigated during moderate hyperglycemia. *Study 3* [13]: Fifteen obese patients investigated before or after intestinal bypass operation. *Study 4* [7]: Thirty-two children in the age range from <1 to 12 years, all suffering from a nephro-urological disorder. Data of the investigated subjects are given in Table I.

Measurement of clearances

Details regarding procedure and determinations of *Cl* and Cl_1 in the 149 subjects are given in part I of our study [10]. Briefly, *Cl* was determined as the ratio between the injected amount of ^{51}Cr-EDTA, Q_0, and the entire area under the plasma concentration curve followed for 4–5 h after the injection by at least 12 blood samplings. The plasma curve was resolved into three or four mono-exponential functions. On the basis of the activity in the plasma samples drawn 3–4 h or 3–5 h after the injection, the intercept c_1 and rate constant b_1 of the final function was calculated by the method of least squares, and the area under the plasma curve from 0 to ∞ was calculated as $\Sigma c_i/b_i$. Cl_1 was determined as the ratio between Q_0 and c_1/b_1.

Estimation of clearances

The following correction formulas were used:

$\mathrm{BM}_{\mathrm{before}}$

$$Cl = 0.9908\cdot Cl_1 - 0.001218\cdot Cl_1^2 \tag{1}$$

(mL/min)

Brøchner-Mortensen correction for one-pool clearance, Cl_1, used *before* normalization to body surface area 1.73 m^2. For adult data only. This was the original formulation by Brøchner-Mortensen [2].

$\mathrm{BM}_{\mathrm{after}}$

$$Cl_{BSA} = 0.9908\cdot Cl_{1,BSA} - 0.001218\cdot (Cl_{1,BSA})^2 \tag{2}$$

$(\mathrm{mL/min/1.73\ m^2})$

Brøchner-Mortensen correction used *after* normalization of one-pool clearance to body surface area 1.73 m^2. For adult data only.

$\mathrm{BM}_{\mathrm{children}}$

$$Cl_{BSA} = 1.01\cdot Cl_{1,BSA} - 0.0017\cdot (Cl_{1,BSA})^2 \tag{3}$$

$(\mathrm{mL/min/1.73\ m^2})$

Brøchner-Mortensen correction for children [7].

Table I. Clinical data of investigated subjects (n=149, M/F/children=71/46/32). For each study, top row is mean value, bottom row is range.

	Age (years)	Height (cm)	Body weight (kg)	Body surface area (m^2)	*Cl* (mL/min)	Cl_{BSA} (mL/min/1.73 m^2)
Study 1, patients	49.6	169.4	68.8	1.80	75.8	72.6
(*n*=69, M/F=40/29)	15–81	148–184	46–102	1.41–2.29	8.2–138	7.5–123
Study 1, normal subjects	26.6	175.5	61.8	1.73	101.2	101.2
(*n*=17, M/F=14/3)	18–47	160–191	54–77	1.59–2.01	74–136	80–134
Study 2	29.1	172.4	60.0	1.69	123.1	126.0
(*n*=16, M/F=13/3)	18–50	161–182	48–70	1.49–1.87	93–186	100–183
Study 3	33.0	166.5	98.0	2.15	124.2	100.6
(*n*=15, M/F=4/11)	22–50	154–188	60–170	1.68–3.06	94–163	76–135
Study 4	6.4	115.4	22.9	0.85	40.4	79.3
(*n*=32, boys/girls=8/24)	0.13–12	49–170	3.4–52.7	0.22–1.57	2.6–88	7.5–123

$\mathrm{BM_{BNMS}}$

$$Cl_{BSA}{=}1.0004{\cdot}Cl_{1,BSA}{-}0.00146{\cdot}(Cl_{1,BSA})^2 \quad (4)$$

$$(\mathrm{mL/min/1.73\ m^2})$$

"Brøchner-Mortensen correction" recommended by the British Nuclear Medicine guidelines for GFR determination [8]. For both children and adult data. The formula is a mean of the above two formulas.

$\mathrm{CH_{0.80}}$

$$Cl = 0.80{\cdot}Cl_1\ (\mathrm{mL/min}) \quad (5a)$$

$$Cl_{BSA} = 0.80{\cdot}Cl_{1,BSA}(\mathrm{mL/min/1.73\ m^2}) \quad (5b)$$

Chantler's correction for using only a single exponential in calculation of clearance (i.e. for using one-pool clearance, Cl_1). Chantler further adds corrections for difference between EDTA clearance and GFR (inulin clearance) and other factors [1]. For both children and adult data. The Chantler correction can be used interchangeably before or after normalization to body surface area 1.73 m^2.

JBM

New correction formula by Jødal & Brøchner-Mortensen [10]:

$$Cl = \frac{Cl_1}{1+f{\cdot}Cl_1} \quad (\mathrm{mL/min}) \quad (6)$$

$$f = 0.0032{\cdot}BSA^{-1.3} \quad (7)$$

or

$$Cl_{BSA} = \frac{Cl_{1,BSA}}{1+f_{BSA}{\cdot}Cl_{1,BSA}}(\mathrm{mL/min/1.73m^2}) \quad (8)$$

$$f_{BSA} = 0.00185{\cdot}BSA^{-0.3} \quad (9)$$

The two versions can be used interchangeably. The formulas are based on theoretical considerations and empirical data, and are expected to give correct results (with scatter around mean values) for all renal functions and all body sizes, for both children and adults.

Assessment of deviations from measurements

For each of the six correction formulas, the deviation of *estimated* Cl_{BSA} (or Cl) from *measured* Cl_{BSA} (or Cl) was expressed relatively (%) and calculated as:

$$relative\ deviation = 100\%{\cdot}\left(\frac{estimated\ Cl_{BSA}}{measured\ Cl_{BSA}} - 1\right) \quad (10)$$

in the 149 subjects. Note that relative deviation will be the same whether calculated on Cl_{BSA} (mL/min/1.73 m^2) or on Cl (mL/min).

Theoretical deviation curves

To assess the impact of body surface area on the deviation, the average deviation as a function of Cl_{BSA} was determined for the given limits of body surface areas in the following way.

First, it was noted that the 2.5 % and 97.5 % percentiles of body surface area in the present 32 children were 0.25 m^2 and 1.47 m^2, respectively. The corresponding figures in the 117 adult subjects were 1.45 m^2 and 2.31 m^2. Rounding to the nearest 0.05 m^2, we find 0.25 m^2, 1.45 m^2 and 2.3 m^2 to be three numbers representing the ranges of body surface area.

Second, for each of the five empirical correction equations (1) to (5), the *estimated* Cl_{BSA} was calculated from a series of values of one-pool clearance ($Cl_{1,BSA}$). With the same values, the *"true"* Cl_{BSA} was calculated with formula (8). Finally, relative deviation of estimated clearance from "true" clearance was calculated and plotted as a function of *"true"* Cl_{BSA}. In the case of the $\mathrm{BM_{before}}$ correction, calculations were made using Cl_1 and equation (6) instead of $Cl_{1,BSA}$ and equation (8). Still, relative deviations are reported as a function of body surface normalized clearance (Cl_{BSA}).

As equation (8) is assumed to give correct mean values (averaged over variable-independent scatter), the curves show the *average* deviation as a function of Cl_{BSA}.

Theoretical deviation table

To compare the "true" relationship (JBM formula) between Cl_{BSA} and $Cl_{1,BSA}$ with that of *estimated* Cl_{BSA} versus $Cl_{1,BSA}$, the levels of *estimated* Cl_{BSA} at which it underestimated the *"true"* Cl_{BSA} by 5 % and 10 % were determined. The value of equality (if any) between *"true"* Cl_{BSA} and *estimated* Cl_{BSA}, and the highest overestimation (if any) of the *"true"* Cl_{BSA} by estimated Cl_{BSA} were also determined.

In children, these assessments were made for body surface areas of 0.25, 0.50, 1.0 and 1.45 m^2, and of 1.45, 1.73 and 2.3 m^2 in adults.

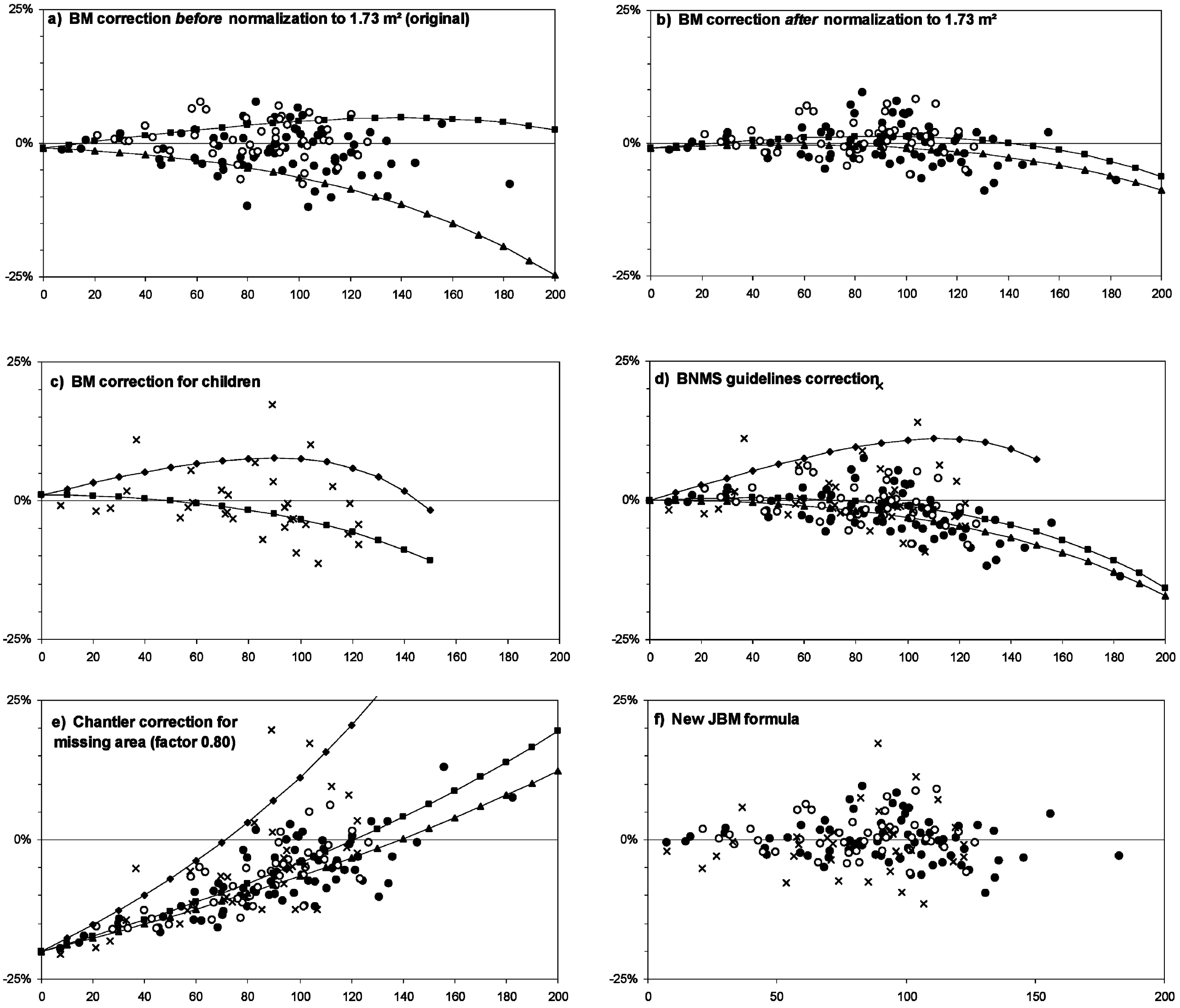

Figure 1. Relative deviation of estimated cleareance as a function of measured clearance (mL/min/1.73 m^2). Legend: • men, ◦ women, × children. Theoretical deviation curves are shown for 0.25 m^2 (diamond), 1.45 m^2 (square), 2.3 m^2 (triangle), assuming new JBM formula to be correct.

Results

The salient data are shown in Figure 1 and in Table II.

BM corrections for adults

In Figure 1a, it can be seen from the theoretical curves that, on average, the BM$_{\text{before}}$ correction in adult subjects with a low body surface area caused *over*estimation of measured clearance in the shown whole range of Cl_{BSA} up to 200 mL/min/1.73 m^2, the maximal overestimation being 5 % (cf. Table II). In subjects with a higher body surface area, the BM$_{\text{before}}$ correction caused increasing *under*estimation of measured clearance with rising clearance level and body surface area.

Figure 1b shows similar data, but for the BM$_{\text{after}}$ correction. Compared to BM$_{\text{before}}$ (Figure 1a), the theoretical deviations are markedly smaller for both small and large subjects. Because of scatter, the difference is less obvious in the measurement data, but overall the measurement data are closer to the zero line in Figure 1b than Figure 1a.

Just below the data for the BM$_{\text{after}}$ correction are shown the data for the BM$_{\text{BNMS}}$ correction (Figure 1d). Both of these corrections are applied on one-pool clearance values already normalized to 1.73 m^2. The underestimations caused by the BM$_{\text{BNMS}}$ correction at clearance values higher than 100 mL/min/1.73 m^2 were larger than the underestimations caused by the BM$_{\text{after}}$ correction

Table II. Comparison of "true" Cl_{BSA} (JBM formula) with five different estimates at different body surface areas.

		Body surface area					
		$0.25\ m^2$	$0.5\ m^2$	$1.0\ m^2$	$1.45\ m^2$	$1.73\ m^2$	$2.3\ m^2$
BM_{before}	Maximal overestimation of "true" Cl_{BSA}				5 %	<1 %	N/A
	Estimated Cl_{BSA} (mL/min/1.73 m^2) when						
	="true" Cl_{BSA}				222	116	N/A
	underestimating by 5 %				236	175	81
	underestimating by 10 %				240	193	117
BM_{after}	Maximal overestimation of "true" Cl_{BSA}				1 %	<1 %	N/A
	Estimated Cl_{BSA} (mL/min/1.73 m^2) when						
	="true" Cl_{BSA}				141	116	N/A
	underestimating by 5 %				182	175	161
	underestimating by 10 %				196	193	186
$BM_{children}$	Maximal overestimation of "true" Cl_{BSA}	8 %	3 %	1 %	1 %		
	Estimated Cl_{BSA} (mL/min/1.73 m^2) when						
	="true" Cl_{BSA}	146	123	77	50		
	underestimating by 5 %	150	141	121	109		
	underestimating by 10 %	150	148	139	132		
BM_{BNMS}	Maximal overestimation of "true" Cl_{BSA}	11 %	5 %	1 %	<1 %	<1 %	<1 %
	Estimated Cl_{BSA} (mL/min/1.73 m^2) when						
	="true" Cl_{BSA}	171	158	115	73	48	10
	underestimating by 5 %	171	168	152	138	130	117
	underestimating by 10 %	168	171	165	158	154	147
$CH_{0.80}$	Maximal *under*-estimation of true Cl_{BSA}	20 %	20 %	20 %	20 %	20 %	20 %
	Estimated Cl_{BSA} (mL/min/1.73 m^2) when						
	="true" Cl_{BSA}	71	88	108	121	127	139
	over-estimating by 5 %	89	110	135	151	159	173
	over-estimating by 10 %	107	132	162	181	191	208

N/A=not applicable (curves do not intersect for values of clearance above zero). Quadratic corrections have no theoretical limit on underestimation. Chantler correction has no theoretical limit on overestimation.

(both theoretically and as seen from the measurements).

BM corrections for children

In small children with a body surface area of 0.25 m^2, the $BM_{children}$ (Figure 1c, upper curve) and BM_{BNMS} (Figure 1d, upper curve) both caused an *over*estimation of measured clearance of up to 8–11 % (cf. Table II). The *under*estimation caused by the two corrections at higher clearance values was largest using the $BM_{children}$ correction.

Chantler correction ($CH_{0.80}$)

Use of the Chantler correction (Figure 1e) caused the largest deviation between measured and estimated clearance in both children and adults. The theoretical cut-off level between under- and overestimation of Cl_{BSA} was from 71 to 121 mL/min/1.73 m^2 in children, and from 121 to 139 mL/min/1.73 m^2 in adults (cf. Table II).

JBM correction

For comparison, deviations between the JBM formula and measured data are shown in Figure 1f. Since the results of the JBM formula are assumed to equal true clearance on the average, theoretical deviation is zero, and the non-zero values from measurement data represent scatter around the average value.

Further results

As part of the Discussion, results are also presented for maximum values of quadratic equations (Table III), values of f and f_{BSA} (cf. equations (7) and (9)) for selected body surface areas (Table IV), and the results of a literature study (Table V). The flow of the discussion made it more convenient to present these data in the Discussion section rather than the Results section.

Discussion

The total ^{51}Cr-EDTA plasma clearance determined from the complete plasma curve or estimated from a

Table III. Maximum values of four quadratic correction equations and corresponding one-pool clearances.

Correction equation	$Cl_{1,BSA}$ mL/min/1.73 m^2	Maximum value of Cl_{BSA} mL/min/1.73 m^2
BM_{before}	407*	201*
BM_{after}	407	201
BM_{BNMS}	343	171
$BM_{children}$	297	150

*mL/min

Table IV. f_{BSA} and f at the approximate 95 % limits of body surface area for children and adults in the present material.

	0.25 m^2	1.45 m^2	2.3 m^2
f_{BSA}	0.0028	0.0017	0.0014
f		0.0020	0.0011

measured one-pool clearance using the JBM correction equation was used in the present study as the "true" measure of the total plasma clearance against which the different correction formulas were tested. In the first part of our study [10], the true relationship between total and one-pool clearance was derived analytically and the parameters involved for children and adults were determined resulting in the common JBM correction used here.

All five tested equations used to correct a measured one-pool clearance to the total ^{51}Cr-EDTA plasma clearance showed that the level of clearance had a significant impact on the accuracy of the resulting value of estimated clearance. In adults, only the BM_{before} correction had any significant influence from the size of body surface area on the accuracy, whereas this was the case for all three correction equations used in children.

Accuracy of quadratic equations

The two quadratic equations used for children ($BM_{children}$ and BM_{BNMS}) showed a tendency toward overestimation of the "true" clearance in the low to normal range of clearance. The overestimation was highest and the range largest for very small children, and could be up to 8–11 % on average. Similarly, the three quadratic equations used for adults (BM_{before}, BM_{after} and BM_{BNMS}) showed overestimation for small to medium-sized persons, although the overestimation was small in most cases.

The level of estimated clearance at which the BM_{before} correction underestimated the "true" clearance by 10 % decreased with rising body surface area from 240 mL/min/1.73 m^2 at a body surface area of 1.45 m^2 to 117 mL/min/1.73 m^2 at a body surface area of 2.3 m^2. In the other correction equations the influence of body surface area was of less importance, and a typical level of 10 % underestimation was 190 mL/min/1.73 m^2 (BM_{after} correction), 150 mL/min/1.73 m^2 (BM_{BNMS} correction in adults), 140 mL/min/1.73 m^2 ($BM_{children}$ correction) and 165 mL/min/1.73 m^2 (BM_{BNMS} correction in children).

Accuracy of Chantler correction

Children and adults showed the same pattern when the Chantler correction was used. At estimated clearance values higher than normal values, the "true" clearance was increasingly overestimated with rising clearance levels. At lower than normal values the pattern was the reverse, i.e. the estimated clearance increasingly underestimated the "true" clearance with falling clearance levels.

Maximum values of quadratic equations

The quadratic correction equations of the form

$$Cl_{BSA} = b \cdot Cl_{1,\,BSA} + c \cdot (Cl_{1,\,BSA})^2$$

or an equivalent form for Cl are parabolic functions with a maximum value. The maximum is reached at $Cl_{1,BSA} = -b/2c$ and has a maximum value of $-b^2/4c$. The values of $Cl_{1,BSA}$ (and Cl_1) and corresponding maximum values of Cl_{BSA} (and Cl) are given in Table III for the four quadratic correction equations tested.

Clinically, these maximum values represent a problem in cases of hyperfiltration. For instance, the maximum value of 150 mL/min/1.73 m^2 found for $BM_{children}$ makes it very difficult to detect hyperfiltration for instance in children with diabetes mellitus. The "true" relationship between Cl_{BSA} and $Cl_{1,BSA}$ (or between Cl and Cl_1) overcomes this problem.

Mathematically, the monotonically rising form of the "true" relationship compared with the parabolic form of the quadratic equations explains in general why underestimation of the "true" clearance increases with rising clearance levels.

Importance of clearance level and size of body surface area

Looking at the new JBM correction equations (6)+(7) for accurate determination of total clearance (Cl), from a given value of one-pool (slope-intercept) clearance (Cl_1), it can be seen that the resulting value of Cl varies with f and thereby with body surface area (BSA). This dependency is not included in the empirical BM_{before} correction equation. Therefore, the mean deviations of empirically estimated clearance from the "true" clearance have relatively large

Table V. Clinical data and results in nine previous studies comparing the total ^{51}Cr-EDTA plasma clearance determined from the complete plasma concentration curve (Cl_{ref}) and estimated from a measured one-pool clearance using BM_{before} for correction (Cl_{est}).

Reference	Population	Cl_{ref} range	Cl_{est} range	$Cl_{est} - Cl_{ref}$ mean ± SD (=0.0, p)	Regression of Cl_{est} on Cl_{ref} (slope=1.0, p) (intercept=0.0, p)	Deviation* of Cl_{est} from Cl_{ref} at upper level of Cl_{ref}
Rehling 1989 [16]	44 with nephr. disorders	20–150 mL/min (read from Fig. 1)	20–145 mL/min (read from Fig. 1)	-1.3 ± 3.5 mL/min ($p < 0.05$)	Y=0.94X+2.3 ($p < 0.05$) ($p < 0.05$)	−4.4 %
Effersøe 1990 [17]	15 with urolog. disorders	19–107 mL/min/1.73 m^2	19–107 mL/min/1.73 m^2	-1.4 ± 5.4 mL/min/1.73 m^2 (NS)	Y=0.88X+7.0 ($p < 0.05$) (NS)	−5.5 %
Fleming 1991 [3]	30 with nephr. disorders	9–120 mL/min/1.73 m^2		-0.5 ± 2.2 mL/min/1.73 m^2 (NS)		
Picciotto 1992 [18]	56 with nephr. disorders	10–150 mL/min		-5.4 ± 4.0 % in 39 with $Cl_{ref} > 30$ mL/min ($p < 0.01$)	Y=0.985X−1.8 (NS) (NS)	−2.7 %
Biggi 1995 [19]	42 with nephr. disorders	42–176 mL/min (read from Fig. 1c)	42–150 mL/min (read from Fig. 1c)	−5.1 mL/min −6.2 % ($p < 0.01$ for both)	Y=0.90X+3.5 (not tested for any of the two)	−8.0 %
Sambataro 1996 [20]	5 with type I and 25 with type II DM	14–120 mL/min/1.73 m^2	16–126 mL/min/1.73 m^2	-2.9 ± 7.4 mL/min/1.73 m^2 ($p = 0.05$)	Y=1.02X−4.3 (NS) (NS)	−1.6 %
Hansen 1998 [21]	Type I DM 44 with microalbuminuria and 32 with diabetic nephr.	61–162 mL/min	63–151 mL/min	-0.6 ± 8.6 mL/min (NS)		
Mårtensson 1998 [22]	46 with nephr. disorders	16–110 mL/min	16–115 mL/min		Y=0.96X+0.7 (not tested for any of the two)	−3.4 %
De Sadeleer 2006 [23]	47 healthy subjects	85–160 mL/min	85–140 mL/min (read from Fig. 3B)	-7.3 ± 7.4 mL/min ($p < 0.01$)		

*Calculated from the regression equation. NS=not significant. DM=diabetes mellitus.

dependency of the body surface area (cf. Figure 1a and Table II).

If surface-normalization is made already at the level of one-pool clearance, i.e. estimation of Cl_{BSA} from $Cl_{1,BSA}$, the corresponding JBM equations are (8)+(9), and the "true" dependency on BSA is expressed through f_{BSA} instead of f. As seen in Table IV, f_{BSA} varies less with body surface area than f, making the dependency on BSA in the BM_{after}, BM_{BNMS} and Chantler corrections less than in the BM_{before} corrections. In Figure 1, this can be seen by comparing BSA dependency for adults in Figure 1b, 1d and 1e with the dependency in Figure 1a.

Thus, for adults, the "residual" BSA dependency is minimal in the empirical corrections based on $Cl_{1,BSA}$. However, f_{BSA} depends more on BSA for children than for adults (cf. Table IV), and in all the empirical corrections used for children the deviation depends on BSA (see Figure 1c, 1d and 1e).

The described conditions and their consequences have not been shown before. Recognition demands determination of the correct relationship between one-pool and total plasma clearance, and the variables involved. This was done in part I of our study, with the finding of the ratio $a/(plasma\ volume) = f$ as the unique link between the two clearances. a (minutes) is the area under the plasma fraction curve *not* used for determination of one-pool clearance. Plasma volume was described as a non-linear function of body surface area, common in children, women and men.

Earlier studies

In two previous studies [9,14], an equation corresponding to our equation (8) was derived. However, in both studies, only a single value of the parameter we call f_{BSA} was determined. Blake et al. [14] found the value $f_{BSA}=0.00155$ as a mean for 49 subjects. Fleming [9] used compartment analysis and data from 10 subjects, and fitted the value $f_{BSA}=0.00170$. Both of these numbers are in line with our results for adult subjects, but do not take into account the dependency of body size, which becomes important for children (cf. Table IV).

In the work by Fleming [9], comparisons were made to the BM_{BNMS} and Chantler corrections. At a *"true"* Cl_{BSA} of 180 mL/min/1.73 m^2, the *estimated* Cl_{BSA} using the BM_{BNMS} correction was found to *underestimate* the "true" clearance by 10 %, whereas it was *overestimated* by 30 % when the Chantler correction was used. The 10 % underestimation for BM_{BNMS} corresponds very closely with our findings: For *"true"* $Cl_{BSA}=180$ mL/min/1.73 m^2, BSA= 1.73 m^2, we find BM_{BNMS} to underestimate by 12 %. However, the overestimation using the Chantler correction in the present study is only 11 % at 180 mL/min/1.73 m^2. The value of the constant factor used in the Chantler correction was not reported by Fleming [9], but his results fit with a value of 0.90, corresponding to the mean value of 0.93 and 0.87 proposed by Chantler et al. in the two studies [1,15] dealing with correction of the one-pool clearance of ^{51}Cr-EDTA to GFR (=inulin clearance). These composite factors are made up of a factor=0.80 (as used in the present study) allowing for the "missing" area under the plasma concentration curve not used for determination of Cl_1, combined with other factors allowing for the underestimation of inulin clearance by ^{51}Cr-EDTA clearance. Since all the tested quadratic correction equations in the present study are assumed to correct for the "missing" area, the corresponding factor of 0.80 was used in the Chantler correction.

Using cited reference search in "Web of Science", 528 and 61 articles were identified with citation of the original method studies in adults [2] and in children [7], respectively. In nine studies on adults [3,16–23], a comparison had been made of the total ^{51}Cr-EDTA plasma clearance determined from the full plasma concentration curve (Cl_{ref}), and estimated from a one-pool clearance using the BM_{before} correction (Cl_{est}). No studies contained a corresponding comparison for children.

Data and results from the nine studies in adults are summarized in Table V. In all nine studies but one [22], the difference ($Cl_{est}-Cl_{ref}$) had been determined and was in each case found to be a little less than 0.0. The difference was significant in five of the studies [16,18–20,23] and non-significant in three [3,17,21]. In six studies [16–20,22], the regression of Cl_{est} on Cl_{ref} was available, and at the upper level of Cl_{ref} ranging from 110 to 176 mL/min, the corresponding Cl_{est} calculated from the regression equations underestimated Cl_{ref} by 1.6 % to 8 % with a tendency to increase with increasing clearance level. These results are consistent with those presented in our present study. The modest underestimation of a few "high" clearance values has apparently not affected the widespread use and acceptance of the algorithm since the publication more than three decades ago.

Conclusion

In the present study in children and adults we have assessed the accuracy of Chantler's correction and of second-order polynomials in the different versions used for correcting a measured one-pool clearance to the total ^{51}Cr-EDTA plasma clearance. Using the Chantler correction, the reference clearance is *underestimated* at clearance levels lower than 100–130 mL/min/1.73 m^2, whereas it is increasingly *overestimated* at higher clearance levels. Using second-order polynomials, the reference clearance is increasingly *underestimated* at high clearance levels (on average 10 % at 175 mL/min/1.73 m^2). For lower clearance levels in small children (body surface area <0.50 m^2), the reference clearance can be *overestimated* by more than 5 %. The same tendency is seen in small adults (body surface area <1.73 m^2) when one of the polynomials is used before normalization of one-pool clearance to 1.73 m^2.

We suggest that the correction equations tested here are replaced by a common correction equation based on the "true" relationship between one-pool clearance and the total ^{51}Cr-EDTA plasma clearance (cf. equations (6) to (9)).

Declaration of interest: The authors report no conflicts of interest. The authors alone are responsible for the content and writing of the paper.

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