Annals of Nuclear Medicine Vol. 16, No. 8, 541–548, 2002

The single-plasma-sample method for determining the glomerular filtration rate with Tc-99m-diethylenetriamine pentaacetic acid in childhood and adolescence: Is it age-dependent?

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The aim of this study is to assess the accuracy of the pre-existing single-plasma-sample method (SPSM) to measure the glomerular filtration rate (GFR) with Tc-99m-diethylenetriamine pentaacetic acid (Tc-99m-DTPA) in children and adolescents. In addition, the age-independent SPSM is evaluated with two algorithms (Bubeck and Russell) applied for Tc-99m-mercaptoacetyltriglycine (Tc-99m-MAG3) SPSM. ***Patients and Methods:*** The study was performed on 14 patients (12 men and 2 women; age range 3 to 19 yr) with renal diseases. Tc-99m-DTPA (5 MBq/kg) was injected intravenously and thereafter blood samples were taken at 5, 15, 60, 90, 120, 150 and 180 min via the indwelling tube. Radioactivity in the injection syringe and plasma was measured by means of a double-well single-plastic scintillation counter. The "true" GFR as a reference was determined by two methods: 1) 2-exponential curve fitting 7 samples (GFR_7) and 2) 1-exponential curve fitting 3 samples between 90 and 150 min (GFR_3) in a slow clearance phase. The GFR_7 and GFR_3 were searched for to the clearance (GFR_1) estimated from a plasma concentration at various sample times by means of 3 equations designed for children (Groth & Aasted, Ham-I and -II) and 3 for adults (Christensen & Groth, Jacobsson, Itoh). ***Results:*** All the SPSM showed close correlations ($r > 0.95$) with the reference methods. Among them, Jacobsson's equation at sample time = 120 min tended to be the most accurate ($r = 0.9826$, RMSE = 7.8 ml/min)). On the other hand, Ham-I's equation at sample time = 120 min was the most accurate, when it was referred to GFR_3 in correction for overestimation ($r = 0.9951$, RMSE = 4.60 ml/min). The Bubeck and Russells' algorithms showed that the regression equation between the GFR_7 and the estimates was different in 2 groups of adults (49 cases) and children/adolescents. ***Conclusion:*** Our study indicates that Jacobsson's and Christensen & Groth's equations designed for adults are also applicable in determining the GFR with Tc-99m-DTPA in children and adolescents. The algorithms applied for age-independent SPSM with Tc-99m-MAG3 appears to be applicable to SPSM with Tc-99m-DTPA in children, adolescents and adults, but the single age-independent equation with Tc-99m-DTPA will need further investigations.

Key words: glomerular filtration rate, plasma clearance, children, Tc-99m-DTPA

INTRODUCTION

THE SINGLE-PLASMA-SAMPLE METHOD (SPSM) is widely used for determining the glomerular filtration rate (GFR) in both adults[1–4] and children.[5–8] For adults, the Christensen & Groth's equation[1,2] is recommended[9] and has proved to be universally applicable[10] and feasible for SPSM with Cr-51-EDTA and iohexol.[11,12] For children and adolescents, the specific pediatric SPSMs such as the Ham's equation[7] are recommended.[9] The SPSMs designed for adults are still under question as to how accurate they are for estimating the GFR in children and adolescents.[13]

In clinical practice, the age-independent equation which is commonly used in both adults and children is

Received July 5, 2002, revision accepted August 26, 2002.

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convenient. Bubeck et al.[14] and Russell et al.[15] reported a simple equation in the SPSM, which is commonly adopted for the quantification of renal tubular function with Tc-99m-mercaptoacetyltriglycine (Tc-99m-MAG3) at all ages. Their algorithms are attractive and encourage further search for a new age-independent equation for estimating the GFR with Tc-99m-diethylenetriamine pentaacetic acid (Tc-99m-DTPA).

The first aim of this study is to assess the accuracy of the 6 pre-existing SPSMs for the determination of GFR in children and adolescents. The second is to evaluate whether both the algorithms put forward by Bubeck et al.[14] and Russell et al.[15] in the SPSM with Tc-99m-MAG3 may be feasible in the determination of GFR with Tc-99m-DTPA. Finally, use of the age-independent equation for estimating the GFR with Tc-99m-DTPA is explored.

PATIENTS AND METHODS

Children and Adolescents

There were 14 patients (12 male and 2 female; age range 3 to 19 years; mean ± sd = 10.7 ± 5.4 years) who were newly enrolled for the present study. They were followed up for renal parenchymal disease with varying degrees of renal dysfunction (range of serum creatinine level from 0.4 to 2.1 mg/d*l*; mean ± sd = 0.89 ± 0.53 mg/d*l*). The study was approved by the hospital ethics committee and informed consent was given by both patients and parents prior to the test.

Patients were hydrated with 5 m*l*/kg water 20 min prior to the examination. Tc-99m-DTPA was labeled in the hospital with a commercially available freeze-dried kit (Daiichi Radioisotope Co., Tokyo, Japan), which had a labeling yield of over 95%. The administered dose was 5 MBq/kg, which was dissolved in 1.5 to 2.0 m*l* of injected solution. Tc-99m-DTPA was administered through an indwelling butterfly needle during infusion of 10 m*l* normal saline solution. Standard renal scintigraphy was carried out in the supine position. Venous blood samples were drawn at 5, 15, 60, 90, 120, 150 and 180 min after the injection through an indwelling needle placed in the opposite arm to the injection. After scintigraphy, the injection site in the arm was scanned with a gamma camera. There was no significant interstitial leakage in any patient. The patients were confined to bed throughout the scintigraphy but neither movement nor oral intake of water and food were restricted during blood sampling. Plasma from 0.1 to 1.0 m*l* was pipetted into the plastic tube and was finally diluted to 1.0 m*l* per tube by adding saline solution when necessary. The total injected dose and plasma radioactivity at each sample time were counted twice with a double-well single-plastic scintillation counter (Aloka, DCM-200, Tokyo, Japan). The radioactive concentration in each sample was determined directly without the dilution procedure.[16]

The reference GFR was determined by means of two mathematical algorithms: 1) an area under the curve method in the 2-exponential curve fitting 7 plasma concentrations (2-exponential method; GFR_7)[17] and 2) a slope and intercept method in the slow clearance phase with 3 samples between 90 min and 150 min (1-exponential method; GFR_3).[16] The plasma clearance (Cluc: calculated directly by the 1-exponential method) was corrected by the composite correction factor of 0.85 (GFR_3 = 0.85∗Cluc) for the overestimation.[5,7,18] The above curve fitting was performed by nonlinear weighted regression with commercially available software (JMP v.4J, SAS Institute, USA). The reference GFRs obtained were compared to the GFR (GFR_1) at various sample times, which were determined by means of 6 SPSMs: 3 designed as specific pediatric equations (Groth & Aasted,[6] Ham-I[7] and Ham-II[8] and another 3 designed for adults (Christensen

Table 1 Linear regression and correlation analysis of the estimate by means of single-plasma-sample method at various sample times against the reference GFR

Method	Sample time (min)	Correlation analysis		Linear regression equation	
		r	RMSE	Intercept	Slope
Groth & Aasted	90	0.9702	9.68	8.857	0.881
	120	0.9784	8.05	7.888	0.865
Ham-I	120	0.9745	10.49	0.396	1.033
Ham-II	120	0.9745	10.60	0.086	1.046
Christensen & Groth	90	0.9747	10.92	−10.953	1.093
	120	0.9884	8.9	−7.088	1.096
	150	0.9807	8.52	0.402	0.969
Jacobsson	90	0.9691	9.70	5.25	0.863
	120	0.9826	7.8	3.142	0.942
	150	0.9801	7.87	4.57	0.882
Itoh et al.	90	0.9716	9.78	−3.704	0.913
	120	0.9806	8.64	−2.422	0.980
	150	0.9753	9.13	2.661	0.916

r: correlation coefficient, RMSE: root mean square error

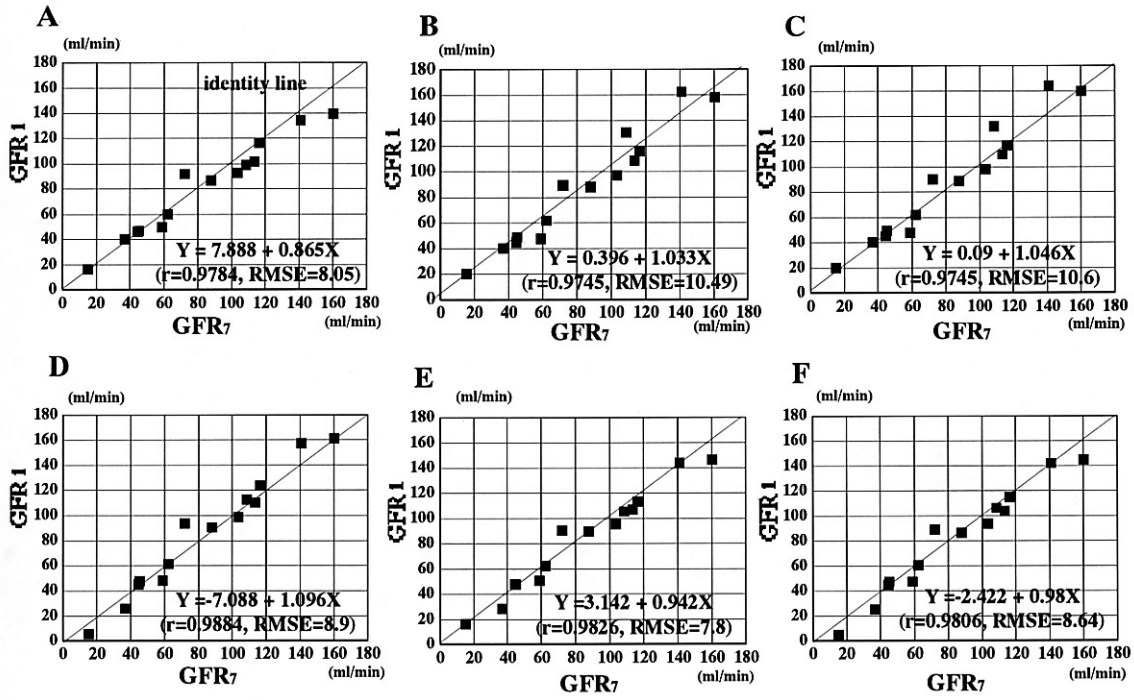

Fig. 1 Scatter plot of the GFR estimated by single-sample-plasma method (GFR_1) at sample time = 120 min against the reference GFR determined by the 2-exponential method (GFR_7). A: Groth and Aasted's method, B: Ham-I's method, C: Ham-II's method, D: Christensen and Groth's method, E: Jacobsson's method, F: Itoh's method

& Groth,[1,2] Jacobsson[3] and Itoh[4]). Details of these are shown in the Appendix. In the two methods (Groth & Aasted and Itoh), the GFR values were calculated as normalized values for a standard body surface area of 1.73 m^2. In order to allow comparison of errors in each SPSM with the reference in the same range, these estimates were finally standardized to absolute values of ml/min. The body surface area was estimated by means of the Haycock's equation.[19]

Adult Patients

The 49 patients who were already enrolled for another study were again evaluated to assess the clinical feasibility of Bubeck[14] and Russell's[15] algorithms for the age-independent equation for the determination of GFR with Tc-99m-DTPA in both adults and children. The reference GFR in all adult patients was determined by means of a 2-exponential curve fit with 10 plasma samples. Details of these were reported previously.[4,10]

Statistical Analysis

The accuracy was evaluated by linear regression and correlation between the reference GFR and GFR_1 estimated by means of each SPSM. The bias and agreement between the reference GFR and the estimated GFR were evaluated by Bland and Altman's analysis.[20]

RESULTS

Accuracy of 6 single-plasma-sample methods with the 2-exponential method as a reference

The GFR_1 estimated with each SPSM at various sample times from 90 to 150 min was compared to the GFR_7 estimated by the 2-exponential method as a reference. All SPSMs correlated closely with the reference method and the correlation coefficients were over 0.97 (Table 1). The preferable sample time in each SPSM was considered to be 120 min after the injection. Among them, the Jacobsson's equation designed for adults was closest (r = 0.9826, RMSE = 7.8 ml/min) in the linear regression and correlation analysis (Fig. 1). In Bland and Altman's analysis at sample time = 120 min, 3 SPSMs (Groth & Aasted, Jacobsson and Itoh) tended to underestimate the reference GFR and another three (Ham-I, -II and Christensen & Groth) tended to overestimate it (Table 2). The mean difference in GFR_1–GFR_7 was smallest in Christensen and Groth's equation (0.94 ml/min) and the standard deviation was smallest in Jacobsson's equation (7.89 ml/min).

Accuracy of 6 single-plasma sample methods with 1-exponential method as a reference

The GFR_1 in each SPSM at sample time = 120 min is plotted against the reference GFR_3 in Figure 2. All the SPSMs also correlated closely with the reference GFR_3.

Table 2 Bland and Altman's analysis of the GFR difference between the estimate by 6 single-plasma-sample at sample time = 120 min and the reference GFR estimated by the 2-exponential method

Methods	Sample time (min)	Difference in GFR (GFR_1–FGR_7)		
		Mean	SD	95% Confidence*
Groth & Aasted	120	−3.35	9.62	−8.91–2.20
Ham-I	120	3.21	10.18	−2.66–9.09
Ham-II	120	3.83	10.36	−2.14–9.82
Chirstensen & Groth	120	0.94	9.47	−4.53–6.41
Jacobsson	120	−1.67	7.89	−6.23–2.88
Itoh et al.	120	−4.11	8.34	−8.93–0.70

*: Mean ± 2SEM (standard error of mean)

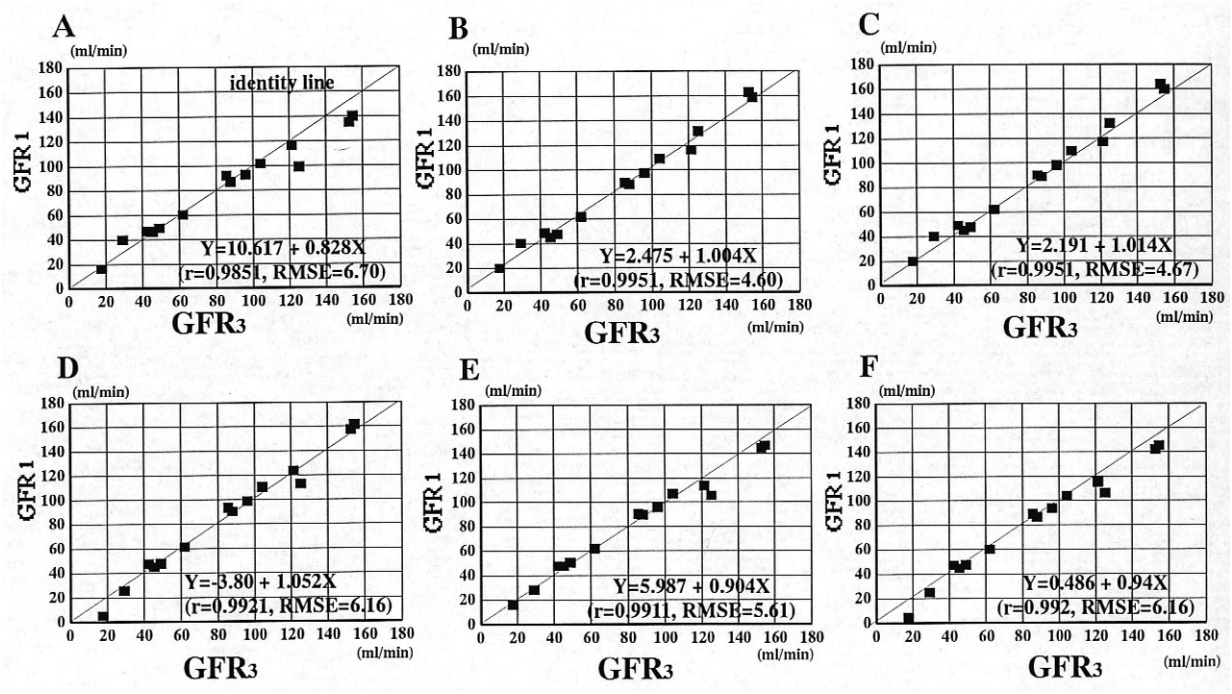

Fig. 2 Scatter plot of the GFR estimated by single-sample-plasma method (GFR_1) at sample time = 120 min against the reference GFR determined by the 1-exponential method with 3 plasma concentrations between 90 and 150 min (GFR_3). A: Groth and Aasted's method, B: Ham-I's method, C: Ham-II's method, D: Christensen and Groth's method, E: Jacobsson's method, F: Itoh's method

Among them, the Ham-I's method showed the closest correlation in linear regression and correlation analysis (r = 0.9951, RMSE = 4.60 m*l*/min). In Bland and Altman's analysis at sample time =120 min, 3 SPSMs (Groth & Aasted, Jacobsson and Itoh) tended to underestimate the reference GFR and another 3 (Ham-I, -II and Christensen & Groth) tended to overestimate it (Table 3). The Christensen & Groth's equation was also smallest in the mean difference (0.55 m*l*/min) and the Ham-I's method was smallest in standard deviation in the GFR difference (4.43 m*l*/min).

Evaluation of Age-Independent Equation

In Bubeck's algorithm, the plasma concentration at sample time is scaled by body surface area and the estimated plasma clearance is expressed as a normalized value (see Appendix). Figure 3A shows scatter plots of the GFR_7 as a reference against these estimates. The relation between them at sample time = 180 min in adults and at sample time = 120 min in children/adolescents shows a linear regression. The regression equations in adults and in children/adolescents were Y = 144.3 – 80.62X (r = 0.989, RMSE = 5.83) and Y = 194.8 – 91.61X (r = 0.965, RMSE = 11.58), respectively. They did not give a single regression equation which are commonly applicable in both adults and children/adolescents.

In Russell's algorithm, the plasma concentration at sampling time is scaled by body weight and the plasma clearance is estimated as the absolute value for m*l*/min (see Appendix). Figure 3B shows scatter plots of Ct/W against –Ln(pW) that were calculated from the plasma concentration at 180 min in adults and at 120 min in

Table 3 Bland and Altman's analysis of the GFR difference between the estimate by 6 single-plasma-sample methods at sample time = 120 min and the reference GFR estimated by the 1-exponential method with correction for overestimation

Methods	Sample time (min)	Difference in GFR (GFR_1–GFR_3)		
		Mean	SD	95% Confidence*
Groth & Aasted	120	–3.74	0.99	–9.51–2.02
Ham-I	120	2.84	4.43	–0.27–5.38
Ham-II	120	3.44	4.53	–0.83–6.06
Chirstensen & Groth	120	0.55	6.36	–3.10–4.42
Jacobsson	120	–2.07	6.88	–6.04–1.90
Itoh et al.	120	–4.51	6.65	–8.35–0.67

*: Mean ± 2SEM (standard error of mean)

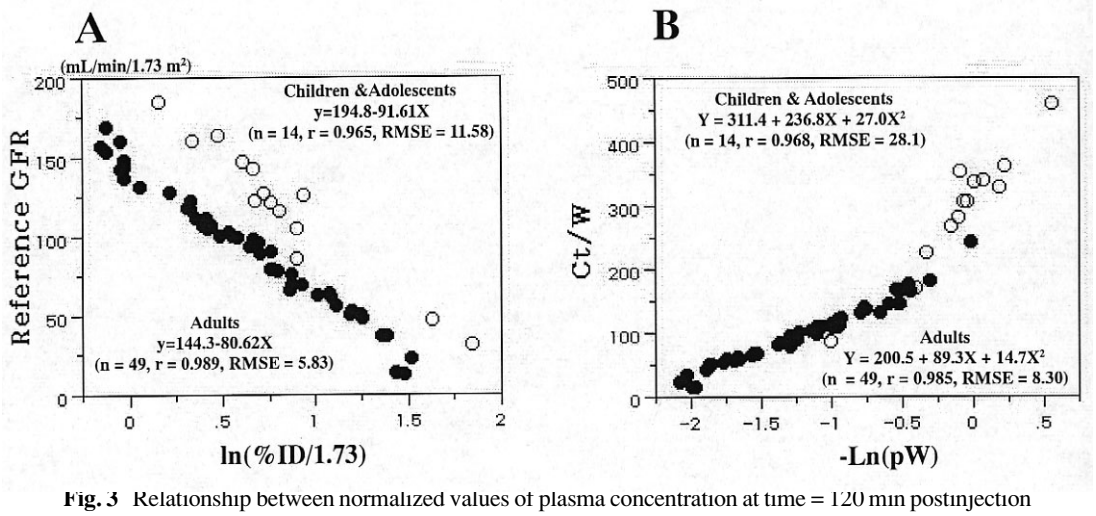

Fig. 3 Relationship between normalized values of plasma concentration at time = 120 min postinjection and the reference clearance determined by the 2-exponential method using Tc-99m-DTPA. The white circle indicates children/adolescents. The black circle indicates adults. A: Bubeck's approach, B: Russell's approach

children/adolescents. The relationship between them in adults and children/adolescents shows a polynomial curve. The regression equations for adults and children/adolescents were $200.2 + 89.3X + 14.7X^2$ (r = 0.985, RMSE = 8.30) and $Y = 311.4 + 236.8X + 27.0X^2$ (r = 0.968, RMSE = 28.1), respectively. They did not show a single regression equation.

DISCUSSION

The "gold standard" for the determination of the GFR has been considered to be continuous infusion of inulin with urine and plasma sampling,[21,22] but this method is technically complicated and is seldom performed in a clinical setting. Plasma clearance after a single injection of a GFR marker has been approached as an alternative to renal clearance of inulin. There are two major algorithms for plasma clearance determination without urine collection in a single injection: 1) 2-exponential curve fitting multiple plasma samples[17,21] and 2) 1-exponential curve fitting plasma samples more than 2 in a slow clearance phase.[5,18,23] In children, the plasma clearance determined by the 2-exponential method with 5 samples within the first 2 hours after the injection was more accurate than that by the 1-exponential method in a slow clearance phase.[23] The 2-exponential method with multiple plasma samples is considered to be the "gold standard" with a single injection technique with the GFR markers in adults and children.[21,23] The multiple plasma sample technique is still cumbersome in practice. Therefore, alternative methods such as the 1-exponential curve fitting two samples and simplified single-plasma-sample method, which were derived from the empirical analysis of the relationship between the reference GFR and the volume of distribution or plasma concentration at sample time are routinely used. The accuracy of each simplified SPSM to determine the GFR should be compared with the 2-exponential method as a "gold standard."

In the present study all the comparative SPSMs showed close correlation with the GFR determined by the 2-exponential method (Table 1). Among them the Jacobsson's equation[3] and Christensen & Groth's equations[1,2] designed for adults appeared to be more accurate than 3 specific pediatric SPSMs (Fig. 1). These results

indicate that two equations designed for adults are applicable to measuring the GFR with Tc-99m-DTPA at all ages. The only limitation in terms of clinical application of these equations to children/adolescents is the optimal plasma sampling time: 120 min in children/adolescents and 180 to 240 min in adults.[1,4] Our results are consistent with the recent report stating that the Jacobsson's equation is applicable to children.[24]

The Jacobsson's equation is based on the volume of distribution at a single sample time and plasma clearance which was determined by the 1-exponential method as corrected by the Brochner-Mortensen's formula. The Brochner-Mortensen's polynomial correction formula for the correction of overestimation in the 1-exponential method is considered to be useful in adults,[25] but was less accurate in children than the Chantler's linear correction formula in our experience. As a matter of fact, the algorithms derived from the Jacobsson's method seem to be contradicted in determining the GFR in children/adolescents. We do not know about the theoretical justification of the Jacobsson's equation that was closest in accuracy in determining the GFR in children/adolescents. On the other hand, the Ham-I's equation was closest to GFR estimated with the 1-exponential method as reference (Fig. 2, Table 3). Their equation was based on the relationship between the volume of distribution and clearance determined by the 1-exponential method with 2 samples between 120 min and 240 min in correcting the composite factor of 0.85 for overestimation.[7] These results are reasonable and could be expected. Nevertheless, their specific pediatric method is not judged to be more accurate than the Jacobsson's and Christensen & Groth's equations designed for adults in estimating the GFR with Tc-99m-DTPA. The results may indicate that the accuracy of SPSMs in measuring the GFR depends on the reference method as the "gold standard."

Renal function in human beings increases in a growth process and decreases after maturation.[26] In order to allow comparison of the GFR in developing individuals with that of adults in a common range, the GFR is expressed as a common denominator for normalization. The body surface area (BSA) is most familiar for normalization of the GFR, while other denominators such as body weight (BW) and extracellular fluid volume (ECV) are considered for normalization of the GFR in children.[27] For the purpose of normalization, there are two algorithms: 1) to estimate a normalized GFR directly by prescaling the plasma concentration (direct estimate) and 2) to estimate the absolute GFR first and thereafter normalize it for body surface area (indirect estimate).[28] Bubeck et al.[14] and Russell et al.[15] applied the age-independent equation for Tc-99m-MAG3 plasma clearance due to normalization of plasma concentration for BSA and BW, respectively. Both algorithms were found to also be useful in estimating the GFR with Tc-99m-DTPA in adults and children/adolescents (Fig. 2). But the regression equation for the two estimates was not common to both groups. It is considered that a direct estimate is theoretically preferable to an indirect estimate.[28] We are not sure which of them is suitable for normalizing the GFR in children/adolescents in clinical practice. Our interest is in an algorithm or SPSM which can be commonly used for the accurate determination of the GFR with Tc-99m-DTPA in children/adolescents and adults, because it is clinically important in a cross-sectional search as well as a longitudinal follow-up of renal function in developing patients with renal diseases. Further investigations will be needed on universally applicable age-independent SPSM to determine the GFR with Tc-99m-DTPA. In addition, the SPSM with Christensen and Groth's equation has been proved to be inaccurate in adult patients with Tc-99m-DTPA clearance less than 20–30 m*l*/min.[1,25,29] These should be researched in further studies in children/adolescents.

CONCLUSION

The single-plasma-sample method (SPSM) designed for adults is applicable for determining the GFR in children/adolescents. The accuracy of each SPSM for GFR determination may depend on reference methods as the "gold standard." Jacobsson's and Christensen & Groth's methods designed for adults seem to be more accurate than the specific pediatric equations for children/adolescents such as Ham's and Groth & Aasted's methods. The algorithms applied for age-independent SPSM with Tc-99m-MAG3 also appears to be applicable to the determination of GFR by SPSM with Tc-99m-DTPA in children/adolescents and adults, but to find a single age-independent equation which can be commonly used for all age groups will require further investigation.

ACKNOWLEDGMENTS

The authors thank all members of the ethics committee of the Fussa Metropolitan Hospital for performing this study, and the nuclear medicine technicians of the Fussa Metropolitan Hospital for their technical assistance in measuring plasma radioactivity.

APPENDIX

1. Groth and Aasted[6]

$Cl\ (ml/min/1.73\ m^2) = A + BX$

$A = -553.124\ln(t) + 3236.76$

$B = 72.295\ln(t) - 425.4$

t = sample time (90–120 min)

$X = \ln[C(t) \times BSA \times 10^7/ID]$

C(t): sample activity at time = t (min)

BSA = body surface area (m^2)

ID = injected dose

Reference method of plasma clearance as "gold standard"

2-exponential curve with 5-points

2. Ham-I[7]

Cl (m*l*/min) = $2.602V_{120} - 0.273$

V_{120} = ID/C_{120} (*l*)

$C_{120} = A(t)e^{(0.008)(t-120)}$

ID = injected dose

t = sample time, 100–130 min

A(t) = actual radioactivity at sample time = t

C_{120} = radioactivity corresponding to sample time = t

V_{120} = volume of distribution at sample time = t

Reference method of plasma clearance as "gold standard"

1-exponential curve fitting 2 samples between 2 and 4 hour with composite correction constant of 0.85

3. Ham-II[6]

Cl (m*l*/min) = $2.63V_{120} - 0.48$

4. Christensen & Groth[1] rewritten by Watson[2]

Cl (m*l*/min) = $(-b + SQRT(b^2 - 4ac))/2a$

$a = 0.0000017t^2 - 0.0012t$

$b = -0.000775t^2 + 1.31t$

c = ECVln(ECV/V(t))

ECV = extracellular volume = 8116.6BSA – 28.2

V(t) = volume of distribution = ID/C(t) (m*l*)

t = sample time (min)

BSA = body surface area (m^2)

ID = injected dose

Reference method of plasma clearance as "gold standard"

2-exponential curve fitting 16 samples from 0 to 300 min following the injection

5. Jacobsson[3]

Cl (m*l*/min) = ln(V(t)/V′)/(t/V′ + 0.0016)

V(t) = volume of distribution at sample time t = ID/C(t)

ID = injected dose

C(t) = plasma radioactivity at sample time = t (cpm/m*l*)

V′ = 0.246BW

BW = body weight (g)

t = sample time (min)

Reference method of plasma clearance as "gold standard"

1-exponential curve fitting 4 samples between 240 and 300 minute-postinjection with Brochner-Mortensen's correction

6. Itoh et al.[4]

Cl (m*l*/min/1.73 m^2) = A + Bln(P(t))

$A = 463.1217 - 3.458t - 0.01205t^2 - 0.000015t^3$

$B = -212.601 + 14251t - 0.001834t^2 + 0.0000062t^3$

P(t) = %ID /1.73

%ID = C(t)/ID × 100

C(t) = plasma radioactivity (/*l*) at sample time (min)

ID = injected dose

t = sample time (120 < t <300 min)

Reference method of plasma clearance as "gold standard"

2-exponential curve fitting 10 samples between 5 and 300 min post-injection

7. Bubeck et al.[14]

TER (MAG3) (m*l*/min/1.73 m^2) = A + Bln(ID/cnt)

$A = -517e^{-0.011t}$

$B = 295e^{-0.016t}$

ID = injected dose (MBq)

t = time of blood sampling post-injection (min)

cnt = normalized plasma concentration at time t (kBq m*l* • 1.73 m^2)

Reference method of plasma clearance as "gold standard"

continuous infusion without urine sample

8. Russell et al.[15]

Ct/W = $222.6 - 168.8X + 52.73X^2 - 11.14X^3$ (m*l*/min)

X = –ln(pW)

C = ^{99m}Tc-MAG3 clearance in *l*/min

t = sampling time (min)

W = body weight (kg)

p = plasma concentration expressed as the fraction of administered dose (/*l*)

Reference method of plasma clearance as "gold standard"

2-exponential curve fitting multi-sample by non-linear weighted regression

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