Annals of Nuclear Medicine Vol. 20, No. 2, 95–98, 2006

Correction factors after having neglected the first exponential in the estimation of chromium-51 EDTA clearance: a reappraisal

Carlos De Sadeleer, Amy Piepsz and Hamphrey R. Ham

Department of Radioisotopes, CHU St Pierre, Brussels, Belgium

The aim of the present work was to evaluate two classical formulae allowing the correction for having neglected the first exponential in the slope-intercept method used for the determination of EDTA clearance, namely the Chantler's linear correction formula (CH) and the Bröchner-Mortensen's quadratic correction formula (BM). First, a comparison study was performed with the two correction formulae, in order to predict the behavior of the calculated clearance, for various levels of renal function. Second, using data obtained from 47 adult patients with normal renal function, the results obtained with the two correction formulae have been compared to the reference technique, namely the biexponential fit. The results of the comparison study indicated that for clearance values lower than 120 m*l*/min, the results obtained using CH were systematically lower than those of BM, whereas for clearance values between 120 and 140 m*l*/min, the reverse was observed. The differences however, never exceeded 8 m*l*/min. The results were quite different when the clearance was higher than 140 m*l*/min, when the difference between CH and BM results increased rapidly, and the BM provided values systematically lower than CH. The clinical study showed that, in the range of normal clearance values, both CH and BM clearances were slightly lower than the results obtained by means of the reference technique. Based on these results, a new specifically designed validation study involving patients with high clearance values is mandatory to determine which of these two correction methods is more accurate, or to devise a better correction formula.

Key words: Cr-51 EDTA, plasma clearance, two sample method, correction formula

INTRODUCTION

It is generally well accepted that glomerular filtration rate (GFR) can be accurately estimated using a Cr-51 EDTA plasma disappearance curve obtained by means of multiple blood samples (BS) and applying a biexponential fit on this curve. Because of the growing need for simplification, one often restricts the model to one single late exponential, requiring only 2 BS. The clearance can then simply be estimated by calculating the slope and the intercept at time zero of this exponential. However, by neglecting the early exponential, GFR is overestimated[1–3] and correction factors have been proposed: the Chantler's linear correction,[2] and the Bröchner-Mortensen quadratic correction.[3] These correction factors are slightly adapted for children.[4,5]

In a recent consensus, both methods of correction were proposed without any clear preference.[6]

The aim of the present work was to evaluate these two formulae of correction. In the first step, a comparison study was ferformed to predict the behavior of the clearance calculated with slope-intercept method and the above two correction factors. In this study, various EDTA clearance levels were introduced. In the second step, using patients' data, the reference technique, namely the multiple blood sample technique, was compared to the slope-intercept method with the two correction factors.

Received March 29, 2005, revision accepted October 24, 2005.

For reprint contact: Carlos De Sadeleer, M.D., Borrekent 51, 9450 Haaltert, BELGIUM.

E-mail: cdesadeleer@skynet.be

MATERIAL AND METHODS

1. Comparison of correction formulae

In order to simulate the clinical situation, a wide range of

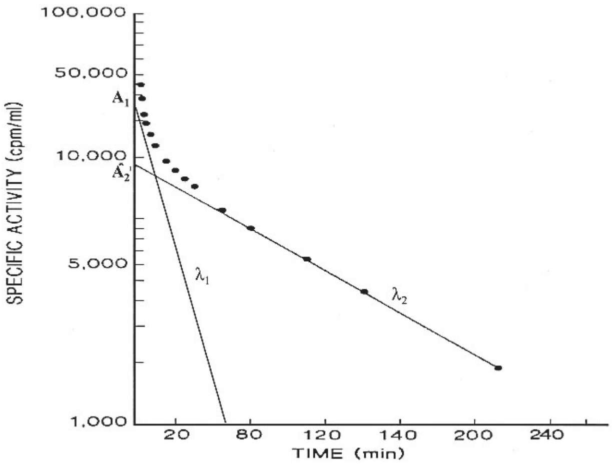

Fig. 1 Example of biexponential fit.

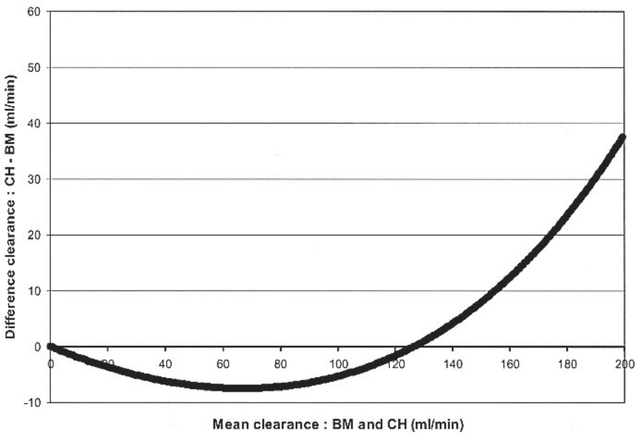

Fig. 2 Comparison of formulae. A Bland Altman plot of the comparison between Chantler's and Bröchner-Mortensen's correction formula is presented. For clearance values lower than 120 m*l*/min, the results obtained using CH were systematically lower than those of BM, with the differences however, never exceeding 8 m*l*/min. For clearance values between 120 and 140 m*l*/min, the reverse was observed. Clearance calculated using BM correction was slightly lower than those obtained using CH. When the clearance was higher than 140 m*l*/min however, the difference between CH and BM results increased rapidly.

clearance values was taken at fixed steps of 1 m*l*/minute. Clearance—as determined by the slope-intercept method—was corrected using both Chantler's linear correction factor and Bröchner-Mortensen's quadratic correction factor.

Chantler's linear correction for adults:

$$Cl_1 = 0.08 \times Cl_2$$

where

Cl_1 = the clearance corrected for the first exponential
Cl_2 = the non-corrected clearance

Bröchner-Mortensen's quadratic correction for adults:

$$Cl_1 = 0.99 \times Cl_2 - 0.0012 \times Cl^2_2$$

where

Cl_1 = the clearance corrected for the first exponential
Cl_2 = the non-corrected clearance

2. Clinical study

From an adult database of normal healthy volunteers, 47 Cr-51 EDTA plasma disappearance curves, obtained with 8 blood samples taken between 5 and 240 minutes after injection, served as the reference technique. The reference renal clearance was calculated using a biexponential fit (Fig. 1). There were 32 males and 15 femles, aged 18 years to 45 years. The selection of healthy volunteers was based only on clinical history and physiological examination. The clearance in this population varied between 85 and 160 m*l*/min. The single compartment model clearance determinations were calculated using the values at 120 min and 240 min.

ANALYSIS

The values of the reference method and the values of the compared method were calculated according to the procedure published by Bland et al.[7]: for each pair of clearance data, individual differences between the two methods were expressed as a percentage of the mean value of the two measurements. The mean of these differences represented the systematic error (bias) between the two measurements. The standard deviation of these differences represented the variability of the technique. A paired t-test was used to evaluate differences between the reference method and the tested compared method. P-values of less than 0.01 were considered to be significant.

RESULTS

1. Comparison of formulae

In Figure 2, the comparison between CH and BM correction is presented. For clearance values lower than 120 m*l*/min, the results obtained using CH were systematically lower than those of BM, with the differences however, never exceeding 8 m*l*/min. For clearance values between 120 and 140 m*l*/min, the reverse was observed. Clearance calculated using BM correction was slightly lower than those obtained using CH. When the clearance was higher than 140 m*l*/min however, the difference between CH and BM results increased rapidly. A clearance of respectively 152, 164, 172 and 180 m*l*/min obtained by CH method corresponded to respectively 145, 152, 157 and 162 m*l* when using BM correction.

2. Clinical study

Both CH and BM (Fig. 3) clearances were found to be

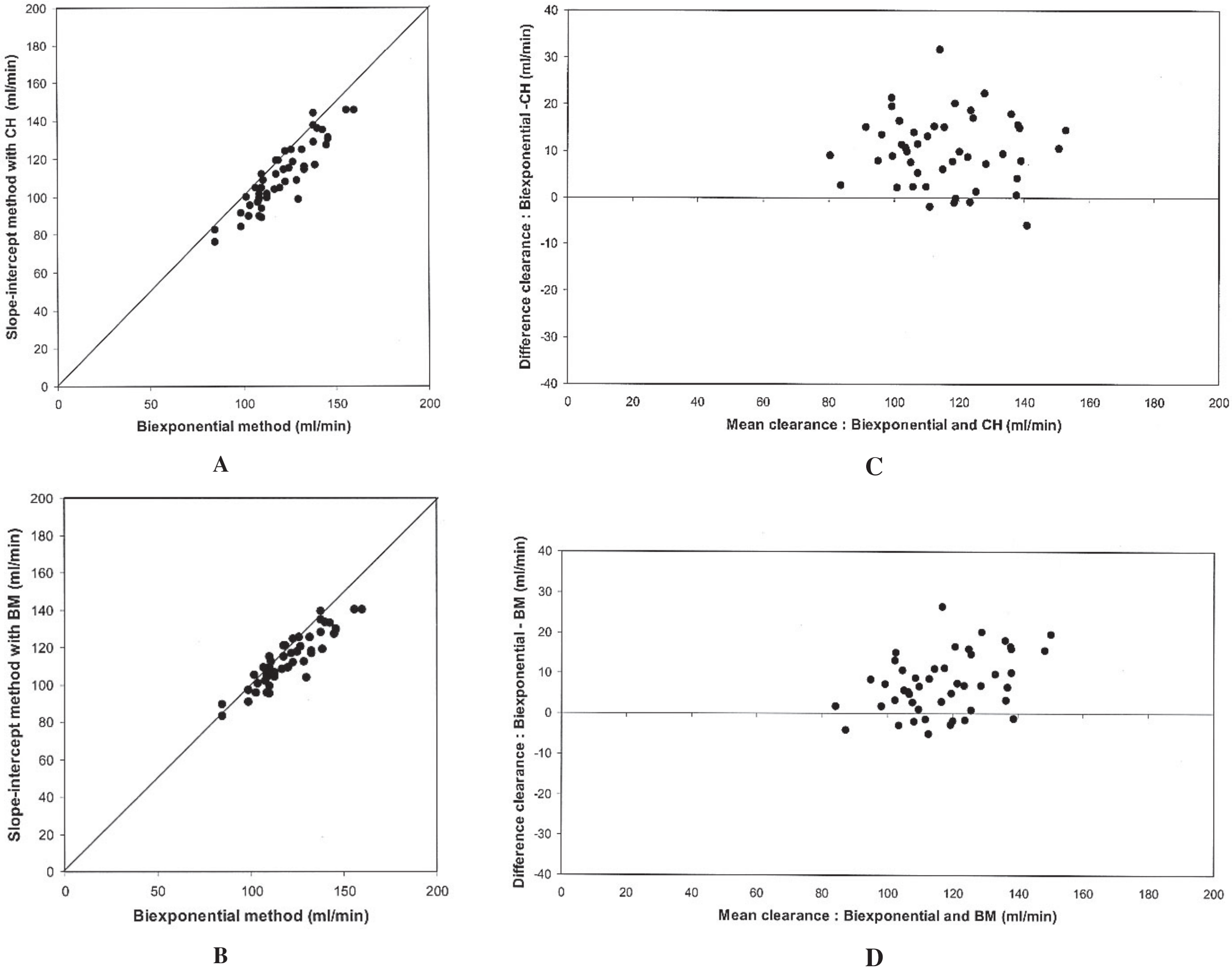

Fig. 3 A: Comparison between clearance determined by Chantler's correction formula and the reference method. Correlation between the reference multiple blood sample clearance (in abscissa) and the slope-intercept method with Chantler's correction factor (in ordinate). The identity line is also plotted. Using Chantler's formula, clearances were found slightly lower than the results obtained by means of multiple sample technique. B: Comparison between clearance determined by Bröchner-Mortensen's correction formula and the reference method. Correlation between the reference multiple blood sample clearance (in abscissa) and the slope-intercept method with Bröchner-Mortensen's correction factor (in ordinate). The identity line is also plotted. Using the Bröchner-Mortensen formula, clearances were found slightly lower than the results obtained by means of multiple sample technique. C: Bland-Altman plot comparing clearance determined by Chantler's correction formula and biexponential fit. In Y-axis the differences between clearance calculated by the biexponential fit and by using Chantler's correction factor are presented. The X-axis represents the mean value of the two clearances. D: Bland-Altman plot comparing clearance determined by Bröchner-Mortensen's correction formula and biexponential fit. In Y-axis the differences between clearance calculated by the biexponential fit and by using Bröchner-Mortensen's correction factor are presented. The X-axis represents the mean value of the two clearances.

sightly but significantly lower than the results obtained by means of multiple sample technique (paired t-test: $p < 0.01$). The mean of differences and the standard deviation of differences were respectively, for CH, 9.9 m*l*/min and 7.5 m*l*/min and for BM, 7.3 m*l*/min and 7.4 m*l*/min.

DISCUSSION

Two compartment model is generally well accepted for accurate determination of Cr-51 EDTA plasma clearance. In clinical practice however, because of the need for simplification, one usually restricts the model to one single late exponential, requiring only 2 BS. The clearance can then simply be estimated by calculating the slope and the intercept at time zero of this exponential. However, by neglecting the first exponential, GFR is overestimated[1] and correction factors have been proposed: the Bröchner-Mortensen quadratic correction[3] and the

Chantler's linear correction.[2] The underlying reason for a non-linear correction is obvious. Indeed the effect of neglecting the first exponential is negligible when the clearance is very low, and it increases non-linearly for higher clearance. The choice of a quadratic correction allows a higher correction for higher clearance but the parabolic shape of a quadratic function could lead, for very high clearance values, to some inconsistency. Chantler proposed a linear correction, using a mean correction factor for a wide range of clearance values. It should be noted that the Chantler global correction factor of 0.93 is a composite correction for various elements including the correction for the early exponential, the discrepancy between standard clearances of inulin and Cr-51 EDTA and the use of venous instead of arterial blood samples.[2] In this work we used a correction factor of 0.80 because we were only interested in correcting the early exponential.[2]

In a recent consensus report, both methods of correction were underlined without any clear preference.[6] However, it is obvious that the two studied correction factors are quite different and will give rise to different results. Numerically however, the magnitude of the differences is not directly obvious from the equations. While the differences between the two methods are rather small for normal or reduced clearance values, they become quite important for clearances higher than 140 m*l*/min. Our data do not, however, allow us to determine which method is more accurate. A specifically designed validation study involving patients with high clearance values is required for this purpose. The need for a new validation study is further underlined by the results we obtained in patients. For clearance values between 85–160 m*l*/min, both CH and BM clearances were found to be slightly lower than the results obtained by means of multiple sample technique. These results are in agreement with the findings of Picciotto et al.,[1] who also found excessive correction by the Bröchner-Mortensen equation, resulting in an underestimation of the clearance compared to the standard method.

The exact reason for this finding is unclear. It could be related to the technique used for calculating the reference clearance. BM correction was devised in the seventies. In that period, the solution of a biexponential fit was obtained using a rather crude peeling technique, instead of a more precise non-linear least square fitting method. The Chantler's correction was established using as a reference method the urinary clearance, which gave lower values than the plasma clearance. It should also been noted that both Chantler and Bröchner-Mortensen correction factors have been devised based on small number of patients, particularly those with high clearance.

CONCLUSION

Chantler's and Bröchner-Mortensen's corrections give different results. While the differences are rather low for clearance values lower than 140 m*l*/min, then become increasingly more important for higher clearances.

Moreover, both Chantler and Bröchner-Mortensen clearances were found to be slightly lower than the results obtained by means of multiple sample technique. A new specifically designed validation study is required, involving a large number of patients covering the whole range of clearance values, including the very high ones. This would allow determining which of these two correction methods is more accurate. It is possible that a new correction formula is necessary.

REFERENCES

1. Piciotto G, Cacace G, Cesena P, Mosso R, Ropolo R, De Filippi PG. Estimation of chromium-51 ethylene diamine tetra-acetic plasma clearance: a comparative assessment of simplified techniques. *Eur J Nucl Med* 1992; 19: 30–35.
2. Chantler C, Garnett S, Parsons V, Veall N. Glomerular filtration rate measurement in man by the single injection method using Cr-51 EDTA. *Clin Sci* 1969; 37: 169–180.
3. Bröchner-Mortensen J. Routine methods and their reliability for assessment of glomerular filtration rate in adults. *Dan Med Bull* 1978; 25: 181–202.
4. Chantler C, Barratt TM. Estimation of glomerular filtration rate from plasma clearance of Cr-51 edetic acid. *Arch Dis Child* 1972; 47: 613–617.
5. Bröchner-Mortensen J, Haahr J, Christoffersen J. A simplified method for accurate assessment of the glomerular filtration rate in children. *Scand J Clin Lab Invest* 1974; 33: 139–143.
6. Blaufox MD, Aurell M, Bubeck B, Fommei E, Piepsz A, Russel CD, et al. Report of the Radionuclides in Nephrourology Committee on Renal Clearance. *J Nucl Med* 1996; 37: 1883–1890.
7. Bland JM, Altman DG. Statistical methods for assessing between two methods of clinical measurement. *Lancet* 1986; II: 307–310.