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Clinical limitations of the estimation of glomerular filtration rate from height/plasma creatinine ratio: a comparison with simultaneous ^{51}Cr edetic acid slope clearance

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SUMMARY A retrospective comparison of single determinations of glomerular filtration rate measured by ^{51}chromium-edetic acid slope clearance (C_{EDTA}) and height/plasma creatinine ratio (Ht/P_C) was undertaken in 199 children aged between 3 and 16 years. Analysis of the data indicated that only if $Ht/P_C \leqslant 1{\cdot}2$ cm/μmol per l was the relationship between Ht/P_C and C_{EDTA} linear. Over this range where renal function is significantly impaired the confidence limits for individual prediction of glomerular filtration rate were so wide that a definitive measurement of renal function would be necessary in clinical practice. Where $Ht/P_C \geqslant 1{\cdot}2$ the relationship was non-linear and the predictive confidence limits very wide. To apply the technique as a screening test for normal renal function ($C_{EDTA} \geqslant 80$ ml/min per $1{\cdot}73m^2$) the Ht/P_C would need to exceed 2·16. In our study this would have detected 57 out of 131 patients who had normal glomerular filtration rates and erroneously included 2 out of 68 with subnormal renal function.

A simple and accurate test of glomerular filtration rate (GFR) would considerably expedite the investigation of children with renal disease. Creatinine clearance techniques rely on complete, precisely timed urine collections which are inherently inaccurate in patients with obstructive uropathy or reflux.[1] Inulin clearance, requiring a continuous intravenous infusion, poses ethical and practical problems and few laboratories routinely measure inulin concentrations. Radioisotope slope clearance studies have been shown to be accurate except in the oedematous patient.[2] They are simple to perform, but require repeated venepunctures and take at least 3 hours, rendering them unsuitable for routine outpatient work.

In a growing child the level of plasma creatinine (P_C) varies inversely with GFR but the relationship is not a simple one and, although GFR per surface area is constant above 3 years of age,[3] endogenous creatinine production and mean P_C levels rise with increasing muscle mass. It appears to be widely accepted that in children 'renal function can be estimated from serum creatinine'.[4] Schwartz *et al.*[5] and Counahan *et al.*[6] each derived the hypothetical relationship between height (Ht) and reciprocal P_C and then confirmed this in studies on three series of patients comparing the estimated with measured GFR by creatinine and inulin clearances and C_{EDTA}. Both groups found the relationship of predicted to measured GFR to be linear and concluded that individual Ht/P_C estimates of GFR were valid.

We have repeated the comparison on 199 children aged between 3 and 16 years whose measured GFRs were distributed between severe impairment and normality. Our results do not accord with previous work.

Method

Between January 1977 and December 1978, C_{EDTA} was performed on 107 boys and 92 girls aged between 3 and 16 years, who simultaneously had plasma creatinine and height measured. Because of the known variation in GFR proportional to surface area that occurs in early childhood[3] children under age 3 years were excluded, as were those who were known to be morphometrically abnormal—for

example those with spina bifida. The height was recorded in cm using a Harpenden stadiometer, and the weight in kg. Surface area was calculated for each child from height and weight using the formulae of DuBois and DuBois[7] and Haycock *et al.*[8] Data were analysed using an ICL 1906A computer with software written for the statistical routines to conform with the methods of Armitage.[9] The slope clearances were performed by single compartmental model analysis, and the result expressed as ml/min per 1·73m² surface area. Two blood samples were taken, the first 2 hours after intravenous injection of isotope, and the second at 3, 4, or 6 hours, depending on the expected GFR. Levels of plasma creatinine were determined by a reaction rate method using a Union Carbide centrifugal analyser on a blood specimen drawn immediately before the injection of isotope, and the result expressed as μmol/l.

Results

The Ht/P_C was plotted arithmetically against C_{EDTA} producing a scatter diagram (Fig. 1). Visual inspection suggests that the relationship was non-linear over the full range. We therefore tested for linearity of the relationship using two methods.

(1) The data were tested in the form:
$\text{Log } C_{EDTA} = \text{Log a} + \text{b Log Ht} + \text{Log } P_C$ as reported previously by Counahan *et al.*[6] in their study of 108 children and adults. These authors found that the coefficients $b = -c = 1$, and concluded that the relationship was linear. We were unable to confirm this but derived the values $b = 0{\cdot}91$, $c = 1{\cdot}16$, the latter differing significantly from unity (Student's t test for b; $t = 0{\cdot}96$; for c, $t = -5{\cdot}80$).

(2) Because in clinical practice the Ht/P_C is used we examined the function:
$C_{EDTA} = a \times (Ht/P_C)^b$ in the form $\text{Log } C_{EDTA} = \text{Log a} + \text{b Log } (Ht/P_C)$, and derived the following relationship:

$$\text{Log}_n C_{EDTA} = 3{\cdot}838 + 1{\cdot}151 \text{ Log}_n (Ht/P_C).$$

The standard error of b is 0·0272 and t test for $b = 1$, $t = 5{\cdot}55$ which is significantly different from unity ($P < 0{\cdot}001$). Retesting with $\text{Log}_n C_{EDTA}$ corrected for surface area using the Haycock, Schwartz, and Wisotsky formula generated the regression equation:

$$\text{Log}_n C_{EDTA} = 3{\cdot}834 + 1{\cdot}152 \text{ Log}_n (Ht/P_C).$$

The difference between the two surface area correction methods was so small that the following data analysis was based exclusively on Dubois.

The 95% confidence limits for individual values of C_{EDTA} from Ht/P_C were derived[9] and these proved to be very wide (Fig. 2). Nevertheless the scatter diagram (Fig. 1) suggests that at low levels of GFR the relationship of C_{EDTA} to Ht/P_C may be

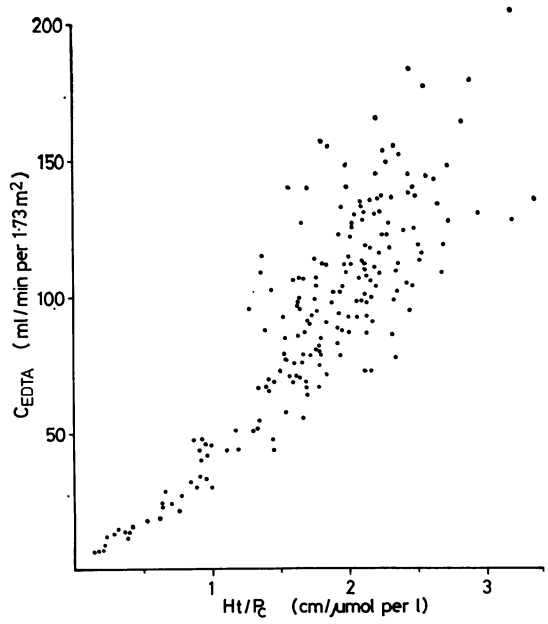

Fig. 1 *Scatter diagram of C_{EDTA} against Ht/P_C in 199 children.*

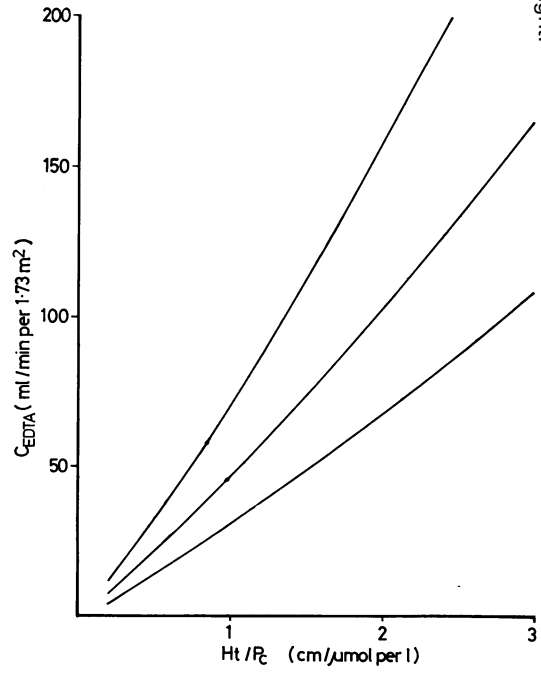

Fig. 2 *Relationship between C_{EDTA} and Ht/P_C showing 95% confidence limits.*

sufficiently linear and the residual variance among the observations sufficiently small to permit interpolation. Testing at successive incremental intervals of Ht/P_C of 0·2 indicated that at $Ht/P_C \leqslant 1{\cdot}2$ the relationship could be reasonably represented linearly with the formula:

$C_{EDTA} = -0{\cdot}78 + 41{\cdot}19\,(Ht/P_C)$.

This is supported by logarithmic analysis as in (2) above, where the regression coefficient b is not significantly different from 1 on this limited section of data (b=0·97, SE=0·049).

Inclusion of observations in the next interval to $Ht/P_C \leqslant 1{\cdot}4$ resulted in a certain loss of linearity in the logarithmic relationship (b=1·096, SE of b=0·059) and widening of the confidence limits (Fig. 3). Above this level linearity was lost.

In Fig. 4, the mean ± 2 standard deviations of C_{EDTA} determinations has been located at the centre of successive Ht/P_C intervals of 0·2 where at least five observations were obtained. This graphically illustrates the abrupt dispersion of data at $Ht/P_C > 1{\cdot}2$.

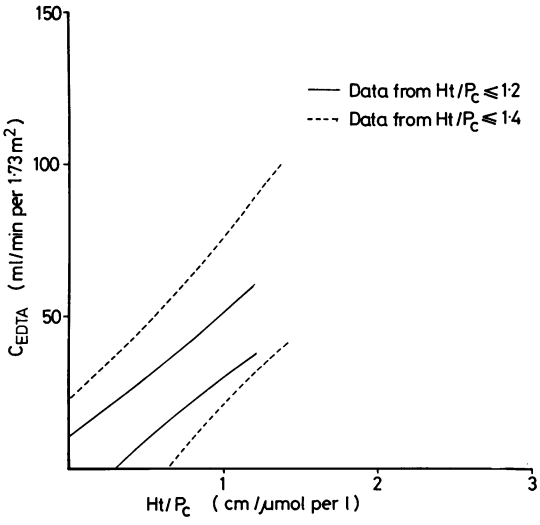

Fig. 3 *95% confidence limits of C_{EDTA} separately derived from individual patient data where $Ht/P_C \leqslant 1{\cdot}2$ and $\leqslant 1{\cdot}4$.*

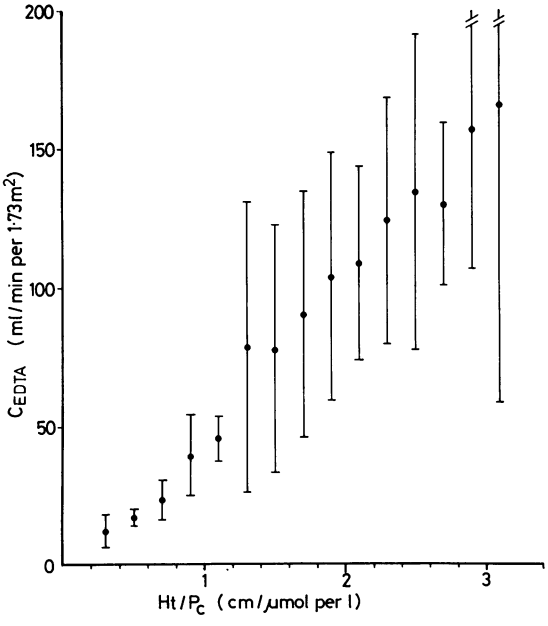

Fig. 4 *Mean±2 SD for C_{EDTA} at 0·2 intervals of Ht/P_C.*

Discussion

In the estimation of GFR in childhood from single Ht/P_C measurements our results do not confirm previously published work and our interpretation reflects this. The relationship between measured and predicted GFR is not linear, although it can be considered so in the small subset of patients with $Ht/P_C \leqslant 1{\cdot}2$. Although a complex function itself would be no bar to the prediction of GFR, the 95% confidence limits are so wide as to render a single estimation highly inaccurate. For example, in an individual with an Ht/P_C of 1·0 the estimated GFR would lie between 31 and 71 ml/min per 1·73m² with 95% probability (Fig. 2). This uncertainty is unacceptable in clinical practice. Even at Ht/P_C of $\leqslant 1{\cdot}2$ where the dispersion of the data is clearly smaller (Fig. 4) and the function can be considered linear, the generated confidence limits, although narrower (Fig. 3), are still too wide to permit accurate prediction. It is within this range of reduced renal function that precise knowledge of GFR is clinically important. Furthermore, the diverging confidence limits at $Ht/P_C \geqslant 1{\cdot}2$ preclude the use of Ht/P_C in screening for normal renal function. Using the lower confidence limit shown in Fig. 2 the Ht/P_C must exceed 2·16 in order to predict an individual GFR ⩾80 ml/min per 1·73m² with 97·5% confidence.

We recognise that the use of C_{EDTA} as the reference standard overestimates actual GFR at normal and high range.[2] This is due to an inherent defect in the single compartmental model which ignores other exponential effects due to the equilibration of radiopharmaceutical between plasma and extracellular space. The non-linearity we have demonstrated between C_{EDTA} and Ht/P_C is in accordance

with this. However, we did not consider it justified to resort to inulin clearance as a reference standard with its additional inconvenience for patients and laboratory. The accuracy of C_{EDTA} in practice is such that the comparison with Ht/P_C is a valid exercise.

We conclude that the prediction of GFR in children from single Ht and P_C measurements is of limited value in clinical practice and should only be applied with caution. With impaired renal function where a precise determination of GFR is essential, the method is too inaccurate. As a screening test for normal renal function it detected 57 out of 131 children but erroneously recognised as normal 2 out of 68 with a measured GFR of less than 80 ml/min per 1·73 m^2. We stress that these conclusions apply only to an individual estimate of GFR; our data do not permit evaluation of sequential measurements of Ht/P_C to monitor rates of change of renal function in a particular patient.

The chemical determinations were carried out in the Department of Clinical Chemistry, under the direction of the late Dr D N Raine, and data processing was performed by R J Lancaster, computer officer, Department of Social Medicine, University of Birmingham.

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