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CHROMIUM -51- EDTA IN THE DETERMINATION OF GLOMERULAR FILTRATION RATE

by

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The glomerular filtration rate (GFR) is a measurement of considerable importance in the assessment of renal function. It is commonly determined from the 24-hour hour endogenous creatinine clearance although it is recognised that this method is prone to error because creatinine may be secreted by the renal tubules. Thus, creatinine clearance may grossly overestimate the true glomerular filtration rate, particularly in the nephrotic syndrome (BERLYNE et coll. 1964). Nevertheless, the use of the endogenous creatinine clearance as a measurement of the glomerular filtration rate remains a most useful tool in the diagnosis of renal disorders.

Radioactive chromium complexed with ethylene diamine tetracetic acid (^{51}Cr-EDTA) appears to fulfil the requirements for an ideal clearance substance (Editorial in Lancet 1965) and has been shown to be excreted similarly to inulin when given by the continuous infusion technique (GARNETT, PARSONS & VEALL 1967) even when the creatinine clearance was markedly elevated compared to the inulin clearance (FAVRE & WING 1968.) As inulin is generally recognised as the standard substance for measuring the glomerular filtration rate, any substance

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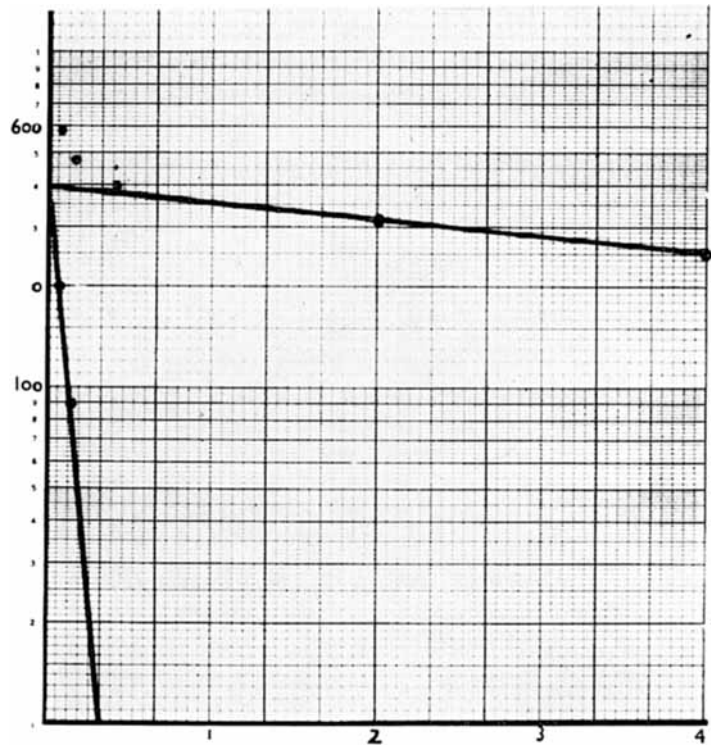

Fig. 1. Semi-log plot of plasma radioactivity (ordinate: in counts per minute) against time (abscissa: hours). The curve is resolvable into two single exponential components.

which gives similar results to inulin over a wide range of values and in all conditions, but without the difficulty of chemical estimations of inulin, seems worthy of investigation.

In this paper we describe a method of determining the filtration rate using a single injection of ^{51}Cr-EDTA, which we believe is suitable for routine hospital ward use; it is not necessary to set up an infusion or to collect urine specimens.

Material and Methods. The ^{51}Cr-EDTA was obtained from the Radiochemical Centre, Amersham, England, and diluted with isotonic saline to give a concentration of 3.5 μCi/ml. Ten millilitres of this solution was administered intravenously to the patient from a pre-calibrated syringe, while 1 ml was diluted with water to 100 ml to serve as a standard. At 5, 10, 15, 120 and 240 minutes after injection, 10 ml of blood was taken, placed in heparinized tubes, and the plasma

separated. These times need not be adhered to rigorously provided the exact time of sampling is noted. Where possible, the urine excreted between the 120-min and 240-min samples was collected and the volume recorded. Four millilitre aliquots of plasma, urine and standard were counted, in a well-type scintillation counter, and corrected for background.

When counts versus time is plotted on semi-log paper, two exponential curves can be resolved, an early mixing phase between plasma and interstitial fluid, (the 'fast' curve) and a later decay due to renal excretion (the 'slow' curve) (Fig. 1).

The glomerular filtration rate was calculated from the following equation (SAPIRSTEIN et coll. 1965)

$$GFR = \frac{1 Y_1 Y_2}{A Y_2 + B Y_1} \tag{1}$$

where $1 =$ total counts in the dose, Y_1 and Y_2 are the slopes of the 'fast' and 'slow' curves, respectively, and A and B are the respective intercepts of the 'fast' and 'slow' curves.

An alternative calculation using the urine collection is based on the method of BIANCHI & TONI (1964)

$$GFR = \frac{X_e}{\int_{t_1}^{t_2} Xp\ (t)\ dt} \tag{2}$$

where X_e is the amount of substance eliminated between t_1 and t_2 and $Xp\ (t)$ is a function describing the change in plasma concentration with time.

Since the curve has become monoexponential by two hours $Xp(t) = X_{120}\ e^{-\lambda t}$ where is the slope of the line and X_{120} is the plasma concentration at 120 minutes. The integral then simply reduces to

$$\frac{X_{120}}{\lambda} \left[e^{-\lambda t_2} - e^{-\lambda t_1}\right] \tag{3}$$

where t_1 and t_2 are 120 and 240 minutes, respectively. For ease of calculation it should be noted that the constant λ is identical with Y_2 of eq. (1).

As these methods of calculation proved somewhat time-consuming, a computer programme was written in Fortran II for use on an IBM 1620 computer (copies are obtainable from the author on request). This programme accepts the raw data from the scintillation counter and computes the glomerular filtration rate by both methods.

Twenty-four-hour creatinine clearances were performed in the Metabolic Laboratory, St. Vincent's Hospital. The eight cases now reported were unselected,

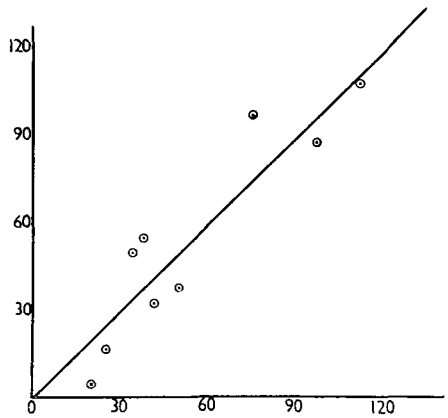

Fig. 2. ^{51}Cr-EDTA clearance (plasma method) (abscissa) versus 24-hour endogenous creatinine clearance (ordinate) $y=0.98x-1.0$; $r=0.91$.

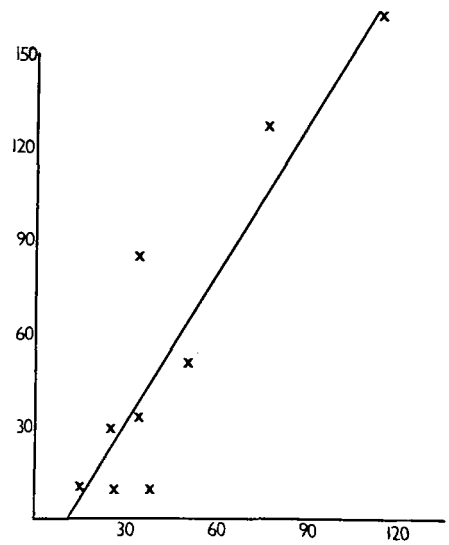

Fig. 3. ^{51}Cr-EDTA clearance (plasma method) (abscissa) versus urine method (ordinate). $y=1.65x-17.6$; $r=0.91$.

and generally referred to the Radioisotope Department for confirmation of an abnormal creatinine clearance or because the creatinine clearance gave an unexpected result.

The results obtained using the plasma disappearance curve against 24-hour endogenous creatine clearances performed about the same time are plotted in Fig. 2.

The correlation between the two methods was $r = 0.914$ and the equation of the regression line $y = 0.984x - 1.03$, where y is the creatinine clearance and x the ^{51}Cr-EDTA clearance. This relationship is as good as that found between inulin clearance and creatinine clearance by FAVRE & WING ($r = 0.908$, $y = 1.28x - 2.49$) who found a very close relationship between inulin clearance and ^{51}Cr-EDTA clearance ($r = 0.992$, $y = 1.02x - 0.95$).

A plot of the ^{51}Cr-EDTA clearance measured by both the plasma disappearance curve and the 2-hour urinary excretion method in nine subjects is presented in Fig. 3. The correlation coefficient between the two methods is again high ($r = 0.91$) but the regression equation $y = 1.649x - 17.63$ shows that the urinary excretion method gives a higher estimate of the clearance over most of the physiologic range.

Discussion

Previous authors (GARNETT et coll. 1967, FAVRE & WING 1968) have shown that the ^{51}Cr-EDTA clearance corresponds very closely with the inulin clearance when estimated by the standard infusion technique, quoting r values of 0.995 and 0.992, respectively. The renal handling of ^{51}Cr-EDTA and inulin would therefore appear to be identical. Since ^{51}Cr-EDTA is not bound by plasma proteins and is not taken up by any organ in the body it does not suffer from the disadvantages of radioactive vitamin B_{12} which for a while had achieved some popularity as an agent for the estimation of the glomerular filtration rate (WEEKE 1968).

The method is not affected by proteinuria or extraneous chromogens in plasma or urine and is particularly useful in cases where urine collection is difficult or impossible, e.g. in incontinent patients. We have used the method successfully to measure glomerular filtration rate in cases of ureterosigmoidostomy and colostomy with concomitant renal disease in whom the collection of urine was impossible. Due to its lack of beta emission the radiation hazard is small. The calculated radiation dose to the kidneys from 35 μCi dose is only 5 mrad, of the same order as the natural background radiation in a week.

GARNETT et coll. (1967) have also reported a series of 32 cases in which the ^{51}Cr-EDTA clearance was measured after single injection and the results compared with the 24-hour endogenous creatinine clearance. They again report a high degree of correlation ($r = 0.948$) but emphasize that the method cannot be used in cases of oedema since equilibration of the complex may take up to 12 hours in such instances.

There is no readily apparent explanation for the increased slope of the line relating the 2-hour urinary excretion method with the plasma disappearance method shown in Fig. 3. Incomplete emptying of the bladder at 2 hours after the injection could account for an increase in the amount excreted between 2 and 4 hours but while this may have occurred in some instances it could hardly account for the regularity of the increase observed.

In practical terms, the greatest source of error in the determination the glomerular filtration rate from the creatinine clearance is incomplete or inaccurate collection of urine. Failure to provide a complete 24-hour collection, particularly when the urine volume is low, would give rise to far greater errors than any arising in the laboratory. While it is not suggested that the method reported here is likely to supplant the 24-hour creatinine clearance it could provide a useful check on the accuracy of creatinine clearances which are clinically doubtful or be used to determine the glomerular filtration rate when the creatinine clearance is difficult or impossible.

The possibility also exists that by monitoring the externally detectable radiation

over the heart the shape of the plasma disappearance curve shown in Fig. 1 could be determined. A single blood sample would then suffice to determine the exact position of the curve since the count rate over the heart would bear a constant relationship to the plasma concentration of the isotope.

It is also possible that ^{51}Cr-EDTA may prove to be a useful substance for renography. Radioiodinated dyes and contrast media may contain a proportion of free iodide or be degraded in the circulation to release iodide which is subsequently taken up by the thyroid. ^{51}Cr-EDTA would appear to be free from any such disadvantagees.

Addendum in proofs

At the expence of some decrease in accuracy the plasma curve method can be simplified by neglecting the initial 'fast' phase and assuming that mixing takes place instantaneously. Eq. (1) then reduces to

$$GFR=\frac{I_{y_2}}{B} \tag{4}$$

using the same notation as before. Only two blood samples are now required, namely those at 120 and 240 minutes. Comparison of twenty clearances calculated by both methods gave a correlation of 0.99 and a regression equation $y=0.82x+6$, where y is the clearance as calculated from eq. (1) and x is the clearance as calculated from eq. (4).

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SUMMARY

A method of determining the glomerular filtration rate from the change in plasma concentration of a single injection of ^{51}Cr-EDTA is described. Results in nine cases are presented and compared with the 24-hour endogenous creatinine clearance. A high degree of correlation was obtained.

ZUSAMMENFASSUNG

Eine Methode, um die Geschwindigkeit der Glomerulusfiltration aus der Änderung der Plasmakonzentration nach einer einfachen Injektion von ^{51}Cr-EDTA zu bestimmen, wird beschrieben. Die Ergebnisse in 9 Fällen werden dargestellt und mit dem 24-Stunden endogenen Kreatinin-Clearance verglichen. Eine hochgradige Korrelation wurde erhalten.

RÉSUMÉ

Description d'une méthode de détermination du taux de filtration glomérulaire d'après les modifications de la concentration plasmatique après une seule injection de ^{51}Cr-EDTA. Les auteurs présentent les résultats obtenus chez neuf malades et les comparent avec la clearance à la créatinine endogène en 24 heures. Ils ont obtenu de hauts degrés de corrélation.

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