Accuracy and reproducibility of a new contrast clearance method for the determination of glomerular filtration rate

P H O'REILLY, P J C BROOMAN, P J MARTIN, A J POLLARD, N B FARAH, G C MASON

Abstract

A new method for determining the glomerular filtration rate was analysed prospectively. The method uses an x ray fluorescence technique to measure disappearance from the plasma of injected non-ionic iodinated contrast media. Eighty seven patients were studied. Fifty four had an intravenous dose of 100 ml iohexol (Omnipaque) and 33 had 50 ml iohexol. Clearances of chromium-51 labelled edetic acid (^{51}Cr-EDTA) were measured simultaneously. In the patients given 100 ml iohexol there was excellent correlation with ^{51}Cr-EDTA clearance (r=0·90). The correlation using 50 ml iohexol was also good (r=0·85). Correlation between creatinine clearance and clearance of ^{51}Cr-EDTA in 33 patients was less satisfactory (r=0·69). There were no adverse reactions to the contrast media. The equipment used for measuring contrast clearance was robust and simple to operate. Freezing plasma samples in 10 studies and re-examining them weekly for six weeks showed no significant variation in results; hence reproducibility was good.

This new and accurate method for determining the glomerular filtration rate merits further study and might find a useful place in routine clinical practice.

Introduction

Determination of the glomerular filtration rate to measure renal function is often required in urological, nephrological, and general medical practice. Currently available methods include inulin clearance, radionuclide studies using chromium-51 labelled edetic acid (^{51}Cr-EDTA) or technetium-99m labelled diethylene triamine penta-acetic acid (^{99m}Tc-DTPA), and creatinine clearance. Because of the complexities of the first two methods clinicians often settle for creatinine clearance or even simple plasma creatinine and urea concentrations as less accurate but more convenient measures of renal function in everyday practice. We present our evaluation of a new method for determining the glomerular filtration rate. This is based on the use of compact, purpose designed equipment currently known as the ELX 84 (Elementanalys AB, Sweden), which measures the disappearance from plasma of injected, non-ionic iodinated contrast media by an *x* ray fluorescence technique.

Materials, subjects, and methods

EQUIPMENT FOR ESTIMATION OF CONTRAST CLEARANCE

The ELX 84 comprises two units. One contains *x* ray fluorescence measuring apparatus, electronics, and a microcomputer, and the other a terminal printer for the transcription of results (fig 1). The *x* ray fluorescence equipment consists of two Americium-241 sources, each with a mass activity of 5·5 GBq (149 mCi) emitting predominantly 60 keV photons. A slot in the top of the unit permits insertion of a test tube containing plasma samples obtained at timed intervals after the injection of contrast. The sources focus their radiation through a collimated lead window. Irradiation of the iodine atoms in the plasma sample causes the emission of characteristic radiation proportional to the plasma iodine concentration and constituting *x* ray fluorescence. This radiation is measured by a sodium iodide detector and registered by a six channel analyser and microcomputer, which then calculates the glomerular filtration rate by reference to a single exponential model of plasma clearance.

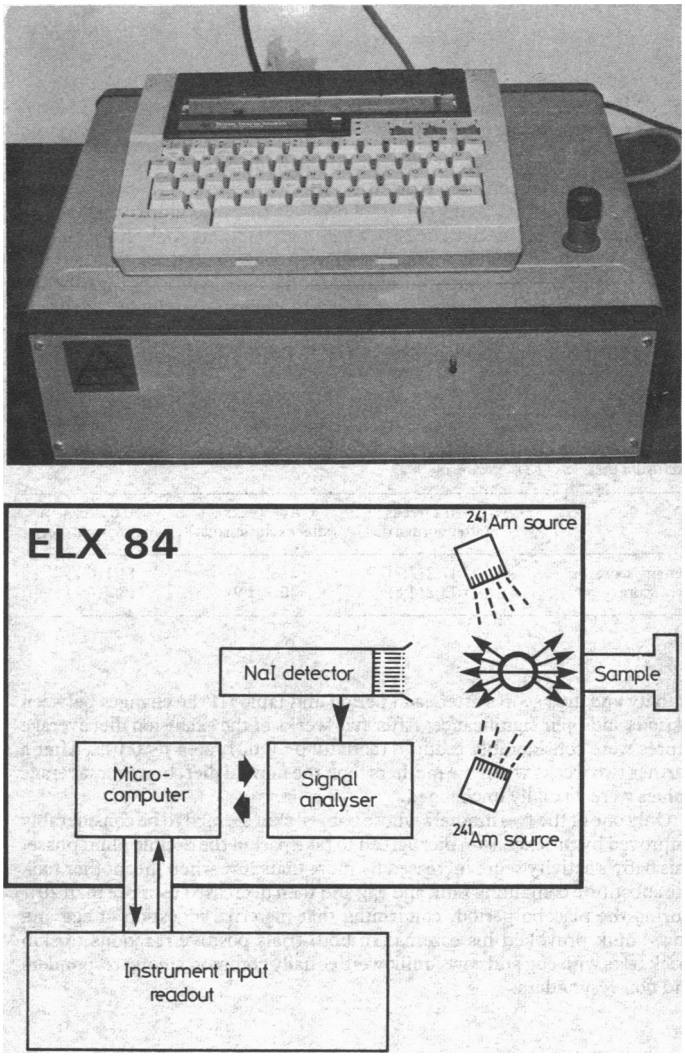

FIG 1—Top: ELX 84 contrast clearance apparatus. Bottom: Schematic representation of composition of contrast clearance apparatus.

METHOD OF ESTIMATING CONTRAST CLEARANCE

The equipment must be calibrated at the beginning of each study day to eliminate errors from possible drifts in electronics and *x* ray fluorescence equipment. Calibration is a simple matter of putting two standard solutions through the machine for analysis, one of sterile water alone and the other

Departments of Urology, Biochemistry, and Radiology, Stepping Hill Hospital, Stockport, Cheshire SK2 7JE

P H O'REILLY, MD, FRCS, consultant urological surgeon
P J C BROOMAN, FRCS, consultant urological surgeon
P J MARTIN, PHD, MRCPATH, consultant chemical pathologist
A J POLLARD, FRCR, DMRD, consultant radiologist
N B FARAH, FRCS, registrar in urology
G C MASON, MB, CHB, senior house officer in urology

Correspondence to: Mr O'Reilly, department of urology.

containing 4 mg iodine/ml. Estimation of the glomerular filtration rate is performed using two plasma samples taken 180 and 240 minutes after the injection of contrast. The contrast must be non-ionic and be handled by glomerular filtration only—for example, iohexol. The exact time of administration and the concentration and volume of the injected agent used are noted, as are the height and weight of the patient. The venous blood samples are taken into heparinised syringes, centrifuged, and a 2·5 ml aliquot of plasma pipetted and transferred into the appropriate bottle for analysis by the ELX 84. This is done by inserting the tubes into the slot in the top of the machine to open the collimated window for analysis, as instructed by the computer. A red light shows during the analysis phase and a green light signals completion. For increased accuracy each specimen may be examined twice, one after the other, noting the time of each analysis.

EVALUATION OF METHOD

Four studies were performed investigating the accuracy of the method. In the absence of any local or regional facility measuring inulin clearance, ^{51}Cr-EDTA clearance was selected as the next most reliable and acceptable standard for comparison.

(1) *^{51}Cr-EDTA clearance versus ELX 84 contrast clearance using 100 ml iohexol*—Fifty four patients (47 men, seven women) aged 25-82 years (mean

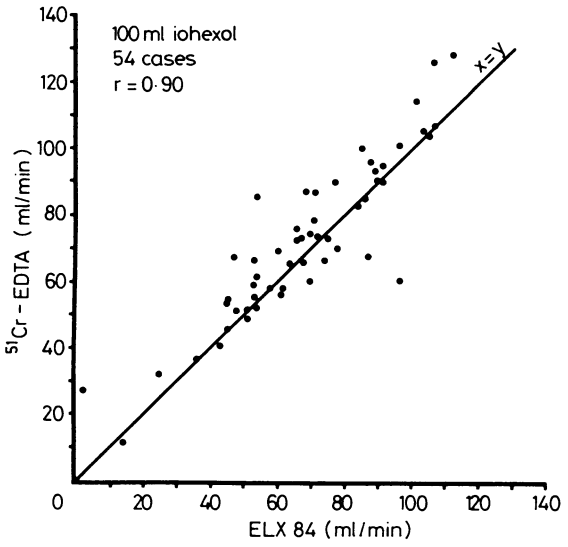

FIG 2—Correlation between ^{51}Cr-EDTA clearance and contrast clearance using 100 ml iohexol in 54 patients.

62) were selected for investigation. They were informed of the purpose of the study and the need for four plasma samples at hourly intervals. Name, date of birth, height (cm), and weight (kg) were recorded. When possible a creatinine clearance estimation was scheduled to end on the day of the study. Through a butterfly cannula inserted into a suitable antecubital vein 2·0-3·7 MBq (54-100 μCi) ^{51}Cr-EDTA was injected and followed by 100 ml iohexol (Omnipaque, Nycomed International/UK). The exact time, concentration, and volume of each injection were noted. Blood samples were taken into heparinised bottles one, two, three, and four hours after injection through a heparinised Venflon cannula inserted in the contralateral arm. The first two samples were of 10 ml, which were centrifuged and kept for ^{51}Cr-EDTA clearance studies. The second two were 20 ml samples, which were centrifuged and divided into two. One sample of each was kept with the first samples for ^{51}Cr-EDTA clearance and the other two were used for ELX 84 contrast clearance. ^{51}Cr-EDTA clearance was calculated by a standard technique using four plasma samples and a two compartment, single exponential "vλ" clearance model with plasma sampling only and calculating the glomerular filtration rate on a volume of dilution principle.[1] ^{51}Cr-EDTA clearance and ELX 84 contrast clearance studies were performed blindly by two independent units. The results were corrected for the patient's height and weight against the standard 1·73 m^2 of surface area and collated blindly by a third independent worker.

(2) *^{51}Cr-EDTA clearance versus ELX 84 contrast clearance using 50 ml iohexol*—Thirty three men aged 17-87 years (mean 66) were examined exactly as above but using only half the dose (50 ml) of contrast medium.

(3) *^{51}Cr-EDTA clearance versus endogenous creatinine clearance*—In 33 cases endogenous creatinine clearance was measured on the urological unit under controlled conditions during the same study period and compared with ^{51}Cr-EDTA clearance to compare the accuracy of this widely practised technique with the method under investigation.

(4) *Reproducibility of data*—The iodine in iohexol is stable in plasma when stored in a sealed tube and frozen. Ten plasma samples from study 2 were collected, frozen at −17°C, and re-examined on the ELX 84 at weekly intervals for six weeks to determine the reliability of the apparatus and reproducibility of the data.

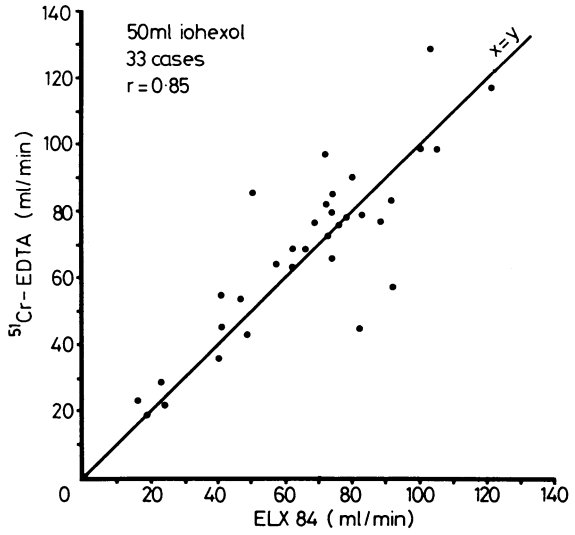

FIG 3—Correlation between ^{51}Cr-EDTA clearance and contrast clearance using 50 ml iohexol in 33 patients.

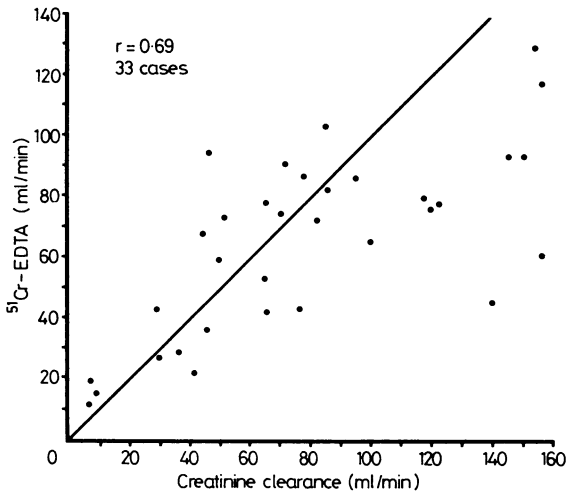

FIG 4—Correlation between ^{51}Cr-EDTA clearance and endogenous creatinine clearance in 33 patients.

STATISTICAL METHODS

Data from studies 1, 2, and 3 were subjected to a standard least squares regression analysis, and data from study 4 subjected to a one way analysis of variance.

Results

Study 1—Figure 2 shows the ^{51}Cr-EDTA clearance versus ELX 84 contrast clearance using 100 ml iohexol in 54 cases. There was a highly significant correlation between the two methods (r=0·90). The correlation was maintained throughout the clinical range, though the ELX 84 consistently underestimated the ^{51}Cr-EDTA value by about 4·2%.

Study 2—Figure 3 shows the ^{51}Cr-EDTA clearance versus contrast clearance using the ELX 84 and 50 ml iohexol in 33 cases. The correlation remained good (r=0·85), though less than when using 100 ml contrast.

Study 3—Figure 4 shows the ^{51}Cr-EDTA clearance versus endogenous creatinine clearance in 33 cases. The correlation was not as good as that obtained from contrast clearance (r=0·69).

Study 4—The results of weekly examinations of 10 samples from study 2 for six weeks by a one way analysis of variance with repeated measurements showed no significant difference at any point. The within and between sample coefficients of variation were 1·9% and 33% respectively.

Discussion

x Ray fluorescence techniques for measuring physiological functions have been used for several years,[2-6] and experiments in animals have shown encouraging results for the determination of renal function.[7] Improvements in the equipment designed for these measurements and the development of non-ionic contrast media raise the possibility of using such a method in routine clinical practice. We have investigated the accuracy of this technique in a clinical series and tried to determine if the method might be suitable for everyday use in radiology or nephrourological units.

The results suggest that the contrast clearance technique is an accurate and simple method for determining the glomerular filtration rate and that it has some advantages over other methods. The prototype equipment is compact and reasonably robust, works on mains electricity, and fits easily on a table top. The only serious problem with the apparatus occurred during extremes of weather when the temperature in the room housing the equipment was occasionally allowed to fluctuate widely. At those times the detection limit of the apparatus tended to rise to levels quite close to the plasma iodine concentrations recorded during the low dose studies. This might lead to inaccuracies in calculating the glomerular filtration rate. The apparatus requires a standard room temperature of between 15° and 25°C. The only other problem of note was a tendency for the printer to break transiently into Swedish if the control settings were inadvertently altered.

After the administration of contrast only two plasma samples are required for the investigation, taken three and four hours after injection. Between the end of the *x* ray examination or injection and the time of sampling no restrictions are placed on diet or activity and patients may leave the department to return later for sampling if necessary (in the same way, for example, as in radionuclide bone scintigraphy). We emphasise that, unlike some other methods, an exact time for venous sampling is not critical; provided that the exact time of sampling is entered at the time of analysis the computer will make allowance for such variations. The venous blood samples should be centrifuged soon after they have been taken, but thereafter they may be frozen if necessary until it is convenient for them to be measured. The examination may initially be combined with urography, though it may be performed without *x* rays. For follow up studies, if imaging is required, the procedure could be used with a limited contrast examination to combine low radiation imaging with the functional study. Since the correlation with ^{51}Cr-EDTA clearance is so good, however, it would be perfectly valid and probably preferable to use radionuclide clearance techniques—for example, ^{99m}Tc-DTPA clearance with divided renal function studies—for follow up comparison with the initial baseline result obtained during the patient's first attendance for urography. The technique seems to be most accurate when 100 ml contrast is used. This is a generous though not excessive dose of iodine (35 g). None the less, the procedure is also very accurate when 50 ml is administered (far more accurate than, for instance, creatinine clearance). Further investigation is needed to see whether an intermediate dose may prove to be the best compromise.

Our findings cast doubt on the common reliance placed on endogenous creatinine clearance as an accurate measure of renal function. The creatinine clearances reported here were obtained on the urological unit under controlled conditions, so the potential for error, particularly in urine collections, was minimal. It seems reasonable to assume that the results in standard outpatient practice would be even less satisfactory.

If there is any disadvantage to the contrast clearance method it is that it requires the intravenous injection of iodinated contrast media. This makes the method most appropriate for use in combination with urography. The serious complication rate from urography using traditional ionic contrast is between one in 40 000 and one in 80 000 examinations.[8-11] It is generally accepted, and has been reported by several international authorities, that the risk of fatal or serious side effects from urography using non-ionic, low osmolar contrast is considerably less.[12 13] In the 87 patients tested here using 100 ml and 50 ml iohexol there was not a single case of a side effect or complication, major or minor.

We conclude that this new method of determining the glomerular filtration rate based on the measurement of iodine clearance after intravenous urography by an *x* ray fluorescence technique appears to be accurate and reproducible and may be a useful addition to existing methods. Evaluation is continuing, but our initial conclusion is that the method might find a useful role in standard clinical practice.

We thank Peter Bell, Vigdis Heggeli, and Stuart Merrett, of Nycomed AS and Co, for the opportunity to evaluate the ELX 84 and for their help during the study. The work would not have been possible without the full and generous cooperation of all the sisters and staff of the urological unit and the departments of nuclear medicine, biochemistry, and radiology at Stepping Hill Hospital. We also thank Mr Brian Farriger, University Hospital of South Manchester, for statistical help and Mr Robert Shields, Manchester Royal Infirmary, for advice on the mathematical aspects of clearance studies.

References

1 Shields RA. Radionuclide techniques for clearance measurements. In: O'Reilly PH, Shields RA, Testa HJ, eds. *Nuclear medicine in urology and nephrology*. 2nd ed. London, Boston, Sydney: Butterworths, 1986.
2 Hoffer PB, Beck RN, Gottschalk A. *Semiconductor detectors in nuclear medicine*. New York: The Society of Nuclear Medicine, 1971.
3 Hoffer PB, Gottschalk MD. Fluorescent thyroid scanning without radioisotopes. *Radiology* 1971;**99**:117-23.
4 Imamura K, Sasaki Y, Sekita N, Someya K, Fujii M. Quantitative in vivo measurement of thyroidal iodine content by static x-ray fluorescence technique. *Invest Radiol* 1979;**14**:316-22.
5 Phelps ME, Grubb JR, Ter Pogossian MM. In vivo regional cerebral blood volume by x-ray fluorescence; validation of method. *J Appl Physiol* 1973;**35**:741-7.
6 Kaufman L, Shames DM, Greenspan RH, Powell MR, Perez Mendez V. Cardiac output determination by fluorescence excitation in the dog. *Invest Radiol* 1972;7:365-8.
7 Gronberg T, Almen T, Golman K, Liden K, Mattison S, Sjoberg S. Non-invasive estimation of kidney function by x-ray fluorescence analysis. Method for in vivo measurements of iodine containing contrast media in rabbits. *Phys Med Biol* 1981;**26**:501-6.
8 Grainger RG. Low osmolar contrast media. *Br Med J* 1984;**289**:144-5.
9 Davies P. Low osmolar contrast media. *Br Med J* 1984;**289**:379-80.
10 Ansell G, Tweedie McK, West CR, Price Evans DA, Couch L. The current status of reactions to intravenous contrast media. *Invest Radiol* 1980;**15**(suppl):S32-9.
11 Fischer HW, Morris TW. Possible factors in intravenous contrast toxicity. *Invest Radiol* 1980;**15**(suppl):S232-8.
12 Higgins CB, Sovak M, Schmidt W, Kelley MJ, Newell JD. Direct myocardial effects of intracoronary administration of new contrast materials with low osmolality. *Invest Radiol* 1980;**15**:39-46.
13 Pfister RC, Hutter AM Jr. Cardiac alterations during intravenous urography. *Invest Radiol* 1980;**15**(suppl):S239-42.

(Accepted 8 May 1986)

Correction

Self poisoning with oral cadmium chloride

We regret that several errors occurred in this article by Dr H M Buckler *et al* (14 June, p 1559). In the last paragraph of the Case report several of the values for cadmium concentrations were incorrect. The last part of the last sentence of this paragraph should have read: "... (blood cadmium 208 μmol/l (23 mg/l), normal range <89 nmol/l (10 μg/l); urinary cadmium 153 μmol/l (17 mg/l); liver cadmium 3·6 mmol/kg (400 mg/kg) wet tissue; lung cadmium 1·7 mmol/kg (200 mg/kg) wet tissue)."

In addition the acknowledgment was omitted. This should have read: "We acknowledge the Poison's Unit at Guy's Hospital, and particularly Mr I M House for performing the cadmium measurements."