Precision of Plasma Clearance of Iohexol for Estimation of GFR in Patients with Renal Disease

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Abstract. The choice of the optimal method for the measurement of renal function is based on the accuracy and the precision of the technique. The plasma clearance of nonradioactive iohexol has been proposed as a reliable alternative to renal clearance of inulin for estimation of GFR. However, the precision of this method in estimating GFR in patients with renal disease has not been determined so far. This issue was assessed by determining plasma clearance of iohexol on three different occasions during a 12-d period in 24 patients with renal disease and a wide range of renal function (creatinine clearance: 14 to 104 ml/min per 1.73 m^2). Overall, the mean intraindividual coefficient of variation was 5.59%, and the reproducibility was 6.28%. The precision of the method also applied to the subgroup of patients with moderate-to-severe renal insufficiency, because a low coefficient of variation (5.71%) and a high reproducibility (6.57%) were found in patients with GFR ≤40 ml/min per 1.73 m^2. It was also shown that the precision of GFR measurement by the plasma clearance of iohexol is not affected by the gender. These findings indicate that the method of plasma clearance of iohexol allows a good precision in the estimation of GFR in patients with normal renal function and different degrees of renal dysfunction. (J Am Soc Nephrol 9: 310–313, 1998)

The development of new therapeutic strategies in nephropathy has led to an increasing demand to precisely estimate GFR, the standard measure of renal function. Inulin clearance, the standard method for measuring GFR, is not practical for routine clinical purposes. It requires continuous intravenous infusion of the marker and urine sampling, sometimes with bladder catheterization of the patient. We recently found that the plasma clearance of the nonradioactive x-ray contrast agent iohexol is a good alternative for the renal inulin clearance technique (1). Analyzing the data with a simplified method that uses a one-compartment model corrected with the Bröchner-Mortensen formula (2), an excellent correlation with the renal clearance of inulin was observed over a wide range of renal function values with very minor errors in predicting GFR (1). In approximately 700 patients, we have also shown that estimation of GFR by a formula that uses a single plasma concentration of iohexol may lead to unacceptable high errors in GFR measurement compared with the multiple-point technique (3).

The choice of the optimal method for the measurement of renal function is based on the accuracy (the error percentage from the true value) and the precision (the time-to-time variability of the test) of the technique. This is an important issue not only for the estimation of GFR in a single subject, but also when the method is used to test hundreds of patients enrolled in multicenter clinical trials with centralized sample processing. The precision of plasma clearance of iohexol in estimating GFR in patients with renal disease has not been determined so far. We sought to establish whether the plasma clearance of iohexol is a precise method as an index of GFR estimation by repeated determinations of this parameter within a short period of time in patients with renal disease and a wide range of renal function.

Materials and Methods

Patients

Twenty-four patients with chronic renal disease (men and women, >18 years old), regularly followed as outclinic patients at the Clinical Research Center for Rare Diseases "Aldo e Cele Daccò", Ranica, Bergamo, Italy, were enrolled. Patients had a wide range of renal function (estimated by creatinine clearance: 14 to 104 ml/min per 1.73 m^2), and their clinical diagnosis included immunoglobulin A nephropathy, focal glomerulosclerosis, and polycystic kidney disease. None were observed with lower urinary tract obstruction or urinary tract infections. Patients with a history of allergy to iodine were excluded from the study. The study protocol was described and explained in detail to all patients before admission, and written informed consent was obtained from each patient, in accordance with the guidelines proposed in the Declaration of Helsinki.

Study Protocol and Procedures

Patients were divided in two groups according to their baseline renal function, estimated by creatinine clearance: group 1 (n = 12) with GFR >40 ml/min per 1.73 m^2; group 2 (n = 12) with GFR ≤40 ml/min per 1.73 m^2. In each group, the number of male and female

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patients was balanced. Assuming a 10% coefficient of variation of the test and a critical difference of 13% between measurements necessary for the difference to be statistically significant (4), we estimated that 10 patients in each group are enough to establish the precision of the test ($\alpha = 0.05$, power = 0.80) (5). To account for dropouts, a total of 12 patients was enrolled in each group.

In all patients, GFR was evaluated on three different occasions with a washout period of 4 d between each observation. After injection of 5 ml of iohexol solution (Omnipaque 300, Nycomed, Milan, Italy) (1), blood samples were taken at 120, 180, 240, 300, 450, and 600 min for patients with an expected GFR ≤40 ml/min per 1.73 m^2, and at 120, 150, 180, 210, and 240 min for those with an expected GFR >40 ml/min per 1.73 m^2 (1). These time schedules were chosen based on an analysis of our previous data (>1000 clearance tests). We found that the GFR values obtained by using these sampling points were the ones that best correlate with renal inulin clearance. Plasma samples were analyzed by HPLC as described previously (1). The plasma profiles were analyzed by a one-compartment open model system, and the calculated clearance of iohexol was corrected according to the Bröchner-Mortensen formula (2).

Statistical Analyses

Results are expressed as mean ± SD and coefficient of variation (CV). The reproducibility (R) of the method was calculated as the mean coefficient of variation as the square root of:

$$\sum_{i=1}^{n} \frac{(CV_i)^2}{n}$$

where CV is the coefficient of variation in subject i for triplicate determinations, and n is the number of subjects. The results were analyzed by t test and paired t test with Bonferroni correction for multiple testing, as appropriate. P values less than 0.05 were considered significant.

Results

Mean GFR measured in the 24 patients on occasion 1 was 47.80 ± 28.41 ml/min per 1.73 m^2, on occasion 2 47.16 ± 27.97 ml/min per 1.73 m^2, and on occasion 3 46.62 ± 28.61 ml/min per 1.73 m^2. These numerical differences were not statistically significant. Similarly, no significant difference in GFR values was found when patients were analyzed separately according to whether renal function was lower or higher than 40 ml/min per 1.73 m^2.

Table 1 shows the mean, SD, and CV for the triplicate determinations of iohexol clearance in all patients. The mean intraindividual overall coefficient of variation in the clearance was 5.59% (range, 1.02 to 12.77%), and the overall reproducibility, R, was 6.28%.

For patients with GFR ≤40 ml/min per 1.73 m^2, the mean intraindividual variation in the plasma clearance of iohexol was 5.71%, and the reproducibility was 6.57%. Similar results were obtained in patients with GFR >40 ml/min per 1.73 m^2 (mean CV: 5.47%; R: 5.98%). When data were analyzed according to gender, both the intraindividual coefficient of variation of the

Table 1. Plasma clearance of iohexol in 24 patients measured on three different occasions

Patient		Iohexol Clearance (ml/min per 1.73 m^2)				
No.	Sex	1	2	3	Mean±SD	CV %
1	F	7.27	7.16	7.44	7.29 ± 0.14	1.94
2	F	18.20	18.32	16.35	17.62 ± 1.10	6.27
3	M	22.13	22.94	23.39	22.82 ± 0.64	2.80
4	F	24.38	20.94	24.73	23.35 ± 2.09	8.97
5	M	20.67	21.21	18.02	19.97 ± 1.71	8.55
6	M	22.73	22.48	22.27	22.49 ± 0.23	1.02
7	F	20.88	18.66	19.49	19.68 ± 1.12	5.70
8	F	26.80	23.87	25.33	25.33 ± 1.47	5.78
9	F	31.61	31.83	32.90	32.11 ± 0.69	2.15
10	M	29.28	35.79	28.55	31.21 ± 3.99	12.77
11	M	32.37	29.28	28.92	30.19 ± 1.90	6.28
12	M	38.78	39.54	35.09	37.80 ± 2.38	6.30
13	F	43.41	44.56	48.82	45.60 ± 2.85	6.25
14	F	36.14	33.23	36.21	35.19 ± 1.70	4.83
15	F	57.86	55.98	51.77	55.20 ± 3.12	5.65
16	M	56.24	54.37	46.02	52.21 ± 5.44	10.42
17	M	66.17	69.50	67.07	67.58 ± 1.72	2.55
18	M	75.31	71.48	72.47	73.09 ± 1.99	2.72
19	F	78.93	84.16	90.36	84.48 ± 5.72	6.77
20	F	72.78	67.91	60.51	67.07 ± 6.18	9.21
21	M	92.94	83.83	90.79	89.19 ± 4.76	5.34
22	M	68.09	76.16	72.42	72.22 ± 4.04	5.59
23	F	104.88	104.49	108.53	105.97 ± 2.23	2.10
24	M	99.39	94.23	91.48	95.03 ± 4.02	4.23

Table 2. Reproducibility of GFR estimation by plasma clearance of iohexol according to gender and degree of renal function

Parameter	Men	Women	GFR ≤40 ml/min per 1.73 m^2		GFR >40 ml/min per 1.73 m^2	
			Men	Women	Men	Women
n	12	12	6	6	6	6
Mean CV %	5.71	5.47	6.29	5.13	5.14	5.80
Range	1.02 to 12.77	1.94 to 9.21	1.02 to 12.77	1.94 to 8.97	2.55 to 10.42	2.10 to 9.21
R %	6.61	5.94	7.35	5.69	5.78	6.18

clearance of iohexol and the reproducibility of the test were comparable. Further stratification of patients by gender and renal function degree failed to reveal any significant difference in mean coefficient of variation and reproducibility (Table 2).

Discussion

The present study documents the low coefficient of variation and the high reproducibility (6.28%) of plasma iohexol clearance, estimated by one-compartment model corrected according to the Bröchner-Mortensen formula (2) after triplicate determination during a 12-d observation period in patients with renal disease and a wide range of renal function. This confirms previous findings reported in 12 healthy subjects in which the reproducibility of iohexol clearance calculated on three occasions as plasma and renal clearances was 8% (6). In the latter study, however, iohexol was given to subjects as constant-rate infusion, whereas we have adopted the single intravenous bolus injection of the contrast agent that further simplifies the procedure and is less cumbersome for the patient. In nine healthy volunteers, a total variation of 11% in iohexol plasma clearance on two different occasions was documented (7). The reproducibility of our single iohexol injection method is also comparable to that of previous observations with ^{51}Cr-ethylenediamine tetra-acetic acid clearance after single injection, being 4% in 25 determinations in five healthy adults (8) and 4% in duplicate determinations in a group of 51 patients (9).

The precision of a method for GFR estimation in patients with renal insufficiency may be reduced, given the possible day-to-day variability of the distribution volume. Our finding of a comparable mean coefficient of variation and reproducibility of plasma clearance of iohexol between patients with GFR ≤40 ml/min per 1.73 m^2 and those with GFR >40 ml/min per 1.73 m^2 indicates that the precision of the present method also applies to patients with severe renal insufficiency. This finding is similar to data of Levey *et al.*, who analyzed the precision of GFR measurements from the variability of measurement to measurement (intertest CV) in all patients participating in the Modification of Diet in Renal Disease multicenter study (10). Among these patients in whom two measurements of GFR by the renal clearance of ^{125}I-iothalamate were performed over a 3-mo interval, the median intertest CV was 6.3%. However, technical difficulties in urine collection have largely contributed to the high intratest coefficient of variation in patients with very low GFR. Thus, while providing comparable, reasonably precise estimations of GFR to renal clearance of ^{125}I-iothalamate, our method offers the advantage of avoiding the use of a radiolabeled tracer and the need for urine collection that may be critical in patients with severe renal insufficiency.

We have also shown that the precision of GFR measurements by the plasma clearance of iohexol is not affected by gender and is not modified by the degree of renal function in male or female patients. Thus, no particular guidelines for a correct and optimal design for this method are required for the two genders.

In summary, we have documented that the plasma clearance of iohexol allows good precision of the estimation of GFR in patients with renal disease and a wide range of renal function. We propose measuring GFR by plasma clearance of unlabeled iohexol (given as a single intravenous injection) as a reliable alternative to renal clearance techniques. Although the requirement of blood sampling beyond 4 h after marker injection to obtain a reliable GFR measurement may be uncomfortable for the patient, this applies only for those with moderate-to-severe renal insufficiency.

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