Assessment of renal function from creatinine clearance measurement and ^{131}I-hippuran renography in cancer patients before chemotherapy

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Background. *Serum creatinine and endogenous creatinine clearance (CrCl) are widely used measures of renal function before prescribing nephrotoxic chemotherapy. This study compares the precision and bias in glomerular filtration rate (GFR) estimation without the need to collect urine by using Cockcroft-Gault formula on a single serum creatinine concentration (CrCo) and ^{131}I-hippuran clearance (HC) determined from the renographic curves.*

Patients and methods. *Fourty-seven patients aged between 27 and 73 years were studied. In all patients, we determined serum creatinine concentration, CrCl, CrCo and HC simultaneously before treatment by combined chemotherapy with cisplatin (CDDP) and in 31 patients, before the third cycle. Serum and urine creatinine concentrations were determined with a Hitachi 911, an automated biochemical analyser. CrCl was calculated from the urine flow, from the ratio between the serum and urine creatinine concentrations and was standardized for the body surface area. Serum creatinine was used to estimate CrCo using a Cockcroft and Gault formula. HC was determined from 131I-hippuran uptake by both kidneys, results were compared to our Nuclear Medicine Department normal values with regard to the age of each patient. For the evaluation of results, Pearson's correlation coefficient and t-test with 95% confidence interval were used.*

Results. *The sensitivity of serum creatinine, CrCo and HC to predict CrCl < 78 mL/min/1.73m^2 was 41%, 68% and 46% and specificity was 95%, 71% and 76% respectively. Value of CoCr for prediction of reduced CrCl (sensitivity) was statistically significantly better than the HC (p=0.03). Value of CoCr for prediction of normal CrCl (specificity) was as good as HC (p=0.3).*

Conclusions. *CrCl for the GFR estimation in the patients treated with nephrotoxic chemotherapy cannot be changed by CrCo and/or HC.*

Key words: glomerular filtration rate, creatinine clearance, renal function; radioisotope renography, iodohippuric acid, ^{131}I-hippuran renography; chemotherapy, cisplatin

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Introduction

Many chemotherapeutic agents can induce renal failure or a specific renal lesion, e.g. in the glomeruli or tubules. Moreover, alternation in the renal function may lead to

impaired metabolism and accumulation of chemotherapeutic agents and their metabolites and can enhance systemic toxicity and renal failure.[1] Cisplatin (CDDP) plays a central role in the treatment of many solid malignant tumors. In addition to many other side effects, an acute and chronic type of renal injury is a result of proximal and probably distal tubule cell necrosis.[2] The nephrotoxicity of CDDP is dose-related and cumulative; it depends on the level of diuresis and pre-existing alternation in renal function. Therefore there is a necessity for early recognition of renal injury for safe and effective usage of this agent.

The glomerular filtration rate (GFR) provides the best overall measure of renal function. The urinary clearance of exogenous substances, such as ^{51}Cr-EDTA and inulin, are accepted as gold standards for the estimation of GFR. However, because of cost and convenience, serum creatinine and endogenous creatinine clearance (CrCl) are the most widely used measures of renal function.[3,4]

Serum creatinine concentration (CrCo) is of limited value in early detection of renal insufficiency because it is well established that it may be seen within normal limits despite more than 50% reduction in GFR. It does not significantly change until CrCl is less than 70 mL/min/1.73m^2 or the inulin clearance is less than 50 mL/min/1.73 m^2.[4,5] CrCl overestimates true glomerular filtration rate (GFR) because creatinine is not only filtrated by the glomeruli but is also secreted by the tubuli.[5] The contribution of tubular secretion to the total CrCl varies widely over time and is increased in those with glomerular disorders.[6]

The measurement of CrCl is easy. It involves collecting a 24 or 48 hour urine, measuring its volume and creatinine concentration in urine and serum. However, collecting the urine for at least 24 hours often cannot be entirely controlled by trained technicians, it is inconvenient for the patients and frequently results in errors.[3,4] Several publications have demonstrated that due to its susceptibility to error, the 24-hour creatinine clearance correlated worse with GFR than the estimates based on serum creatinine.[3,7-9]

The estimation of GFR from the plasma creatinine, using Cockcroft and Gault formula, avoids the need to collect urine.[10] It provides a better estimate of GFR than the plasma creatinine alone because age, gender and bodyweight as determining factors of muscle mass are taken into account.[11,12] The assesment of renal function by Cockcroft and Gault equation was safely used by many oncologists before administering a low weekly dose of cisplatin.[13]

Renography with radioactive ^{131}I-hippuran provides us with renography curves, which show isotope uptake by the kidneys.[14] The technique is short, simple, fairly harmless for the patient and provides a comparison of the function of the two kidneys. Hippuran is excreted exclusively by the kidneys; 20% is filtrated by the glomeruli and 80% by the renal tubules. It is not reabsorbed into the blood. After the intravenous injection of hippuran marked with radioactive iodine, the g-ray detectors are counting the course of hippuran clearance (HC) by curve-drawing; this record is called renogram. From the shape of the curves, data on excretion disorders, tubule impairment and renal circulation are obtained. Good correlations were noted between different parameters of the averaged renogram curves and kidney function parameters (creatinine clearance,[14] inulin and PAH clearance[15,16]), especially after values are standardised for age of the patient. With comparing calculated vs. age-standard value of hippuran clearance, quantitative value of renal function is available.

In the present study, we investigated how accurately and precisely GFR can be approached using plasma creatinine, Cockcroft formula or renography hippuran clearance estimation in comparison with CrCl. The study group was confined to the

patients with normal and mild to moderate impairment of renal function because accurate information on GFR is particularly important in treatment decision-making in nephrotoxic chemotherapy.

Patients and methods

Patients

Fourty-seven patients with malignant melanoma, gastric cancer and ovarian cancer (16 males and 31 females), aged between 27 and 73 years (mean 55) were studied. Half of the patients had metastatic disease and the other half was without evidence of disease after radical surgical treatment. All except 5 patients with impaired renal function were treated by combined chemotherapy with CDDP as adjuvant or palliative setting. Before treatment, all patients were without clinical evidence of serious internal disease and they didn't receive any diuretics or drugs known to interfere with creatinine secretion. No change in nutrition (meat ingestion), hidration rate or daily physical activity was observed. Their body weight ranged from 46 to 114 kg (mean 73) and their body surface from 1.4 to 2.3 m^2 (mean 1.8).

Study design

In all patients serum creatinine, CrCl and HC before treatment and, in 31 patients, before the third cycle were determined. All together, we obtained 78 measurements. A twenty-four hour urine collection on an inpatient basis was carefully controlled by trained technicians. The patients were instructed to begin the 24-hour urine collection in the morning, discard their first voided urine and then collect all their urine for the next 24-hours. In the morning of the second day when urine collection was finished, blood samples for serum creatinine were taken before breakfast. CrCl and CrCo were calculated using that morning creatinine. On the basis of their CrCl values, normalized for body surface, the measurements were divided into two groups: group A (n=41) with CrCl ≥78 mL/min/1.73m^2, and group B (n=37) with CrCl < 78mL/min/1.73m^2. Renography was performed 2 to 6 hours after the urine collection was completed.

Laboratory methods

Serum and urine creatinine concentrations were determined enzymatically by spectrometric method (reagents Boehringer Mannheim, Germany) with a Hitachi 911, an automated biochemical analyser. CrCl was calculated from the urine flow, from the ratio between the serum and urine creatinine concentrations and was standardized for the body surface area:

$$\text{CrCl} = \frac{[\text{urine creatinine concentration (mmol/L)}] \times [\text{urine flow (ml/min)} \times 1.73\ (\text{m}^2)]}{[\text{serum creatinine concentration (mmol/L)}] \times [\text{body surface area (m}^2)].}$$

In addition, the serum creatinine was used to calculate a Cockcroft and Gault estimate of the CrCl using the formula:

$$\text{CrCo (ml/min)} = \frac{[140 - \text{age (years)}] \times [\text{body weight (kg)}] \times [0.85 \text{ for women}]}{[49] \times [\text{serum creatinine concentration } (\mu\text{mol/L})]}$$

Because of different relative amounts of fat and muscles in women, a 15% reduction of a Cockcroft and Gault is recommended in women.[10]

Radiograpy was done without special preparation of the patient (only good oral hydration), using three detectors (both kidneys and the heart). After bolus injection of 100 mCi of sodium o-iodohippurate-^{131}I a continuous tracing was recorded for 15 minutes. For clearance determination, combined figures for parameters from 5 to 15 minutes were obtained by automatically averaging values from right and left renograms by computer. Renograms were also interpreted by visual

inspection of the images to qualitatively assess renal function and technical adequacy of the test.

Statistical analysis and reference values

In the evaluation of results Pearson correlation coefficient and t-tests with 95% confidence interval were used. The statistical analysis was performed using the program Statistica for Windows, version 4.3, StatSoft Inc., 1993.

Reference values were set according to Slovenian National Board for Clinical Chemistry and Clinical Biochemistry Guidelines. The normal serum concentrations irrespective of sex and age are: serum creatinine 44 do 97 µmol/L, CrCl 1.3 do 2.0 ml/s (78-120 ml/min).

Table 1. Patients characteristics

Characteristic	Mean	Range
Age (years)	55	27-73
Serum creatinine (µmol/L)		
Men (n=16)	91	68-193
Women (n=31)	96	62-367
Body surface area (m^2)	1.8	1.4-2.3
Weight (kg)	73	46-114
Hight (cm)	164	152-194
Endogenous creatinine clearance (ml/min)		
A (≥ 78 (n=41))	96	78-145
B (< 78 (n=37))	53	15-76
Hippuran clearance estimation (ml/min)	498	170-1170
Estimation of endogenous creatinine clearance by Cockcroft and Gault formula (ml/min)	80	21-153

Results

In 41 samples in group A (creatinin clearence ≥78 mL/min/1.73m2), the serum creatinine ranged from 62 to 110 µmol/L (mean 82 µmol/L). In 37 samples in group B (creatinin clearence < 78 mL/min/1.73m2), the serum creatinine ranged from 62 to 367 µmol/L (mean 107 µmol/L). Table 1 shows the characteristics of the 47 study participants.

The comparison of CrCl with the serum concentration of creatinine, the CrCo estimation of CrCl and HC estimation of renal function is shown in Table 2. The serum creatinine was elevated above reference values in 17 samples and CrCo and HC were reduced below reference values in 37 and 27 measurements, respectively. In group B the serum creatinine concentration was within normal range in 22 out of 37 cases. The sensitivity of serum creatinine concentration to predict CrCl < 78 mL/min/1.73m2 was 41% (95% confidence interval (CI) 31-50). The specificity was 95% (95%CI 74-100). The correlation coefficient between CrCl and the serum creatinine concentration was 0.48 (p=0.1).

In group A CrCo was reduced in 12 of 41 measurements and in group B was normal in 12 of 37 measurements. The sensitivity of CrCo to predict CrCl < 78 mL/min/1.73m2 was 68% (95%-CI 52-83) and specificity 71% (95%CI 57-85).

The comparisson of CrCl and HC showed that HC was reduced in 10 of 41 cases in group A and it was within normal range in 20 of 37 cases in group B. The sensitivity of HC for prediction of CrCl < 78 mL/min/1.73m2 was 46% (95%CI 30-62) and specificity 76% (95%CI 62-89).

As shown in Figures 1 and 2, the relationship between the CrCl and CrCo or HC was analyzed according to the expectation of an ideal case where CrCl is equal to GFR. By plotting values of CrCo or HC (y) versus GFR(x) as determined by CrCl, linear regression showed rather weak correlation between CrCl and GFR estimation by CrCo or HC. The correlation between CrCl and CrCo was slightly better (r=0.6) than the correlation between CrCl and HC (r=0.55), but the difference was not significant.

The prediction of CrCl < 78 mL/min/1.73m2

Table 2. Comparison of endogenous creatinine clearance with serum concentration of creatinine, estimation of endogenus creatinine clearance using Cockcroft and Gault formula and estimation of glomerular filtration rate by hippuran clearance in 78 concomitant measurements

	S-creatinine		CrCo		HC	
	normal	elevated	normal	reduced	normal	reduced
No of measurements	61	17	41	37	51	27
CrCl						
A (≥ 78 ml/min)	39	2	29	12	31	10
B (< 78 ml/min)	22	15	12	25	20	17

CrCl - endogenous creatinine clearance, S-creatinine - serum concentration of creatinine, CrCo - estimation of endogenous creatinine clearance by Cockcroft and Gaut formula, HC - ^{131}I-hippuran clearance estimation

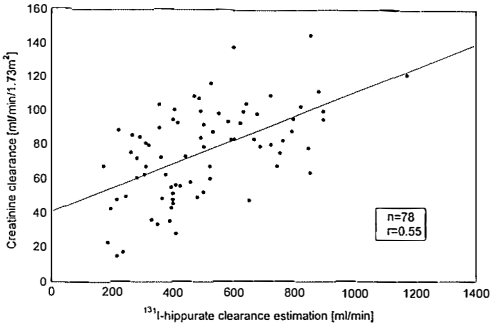

Figure 1. Correlation between creatinine clearance and estimation of ^{131}I-hippurate clearance in 47 patients and 78 simultaneous determinations.

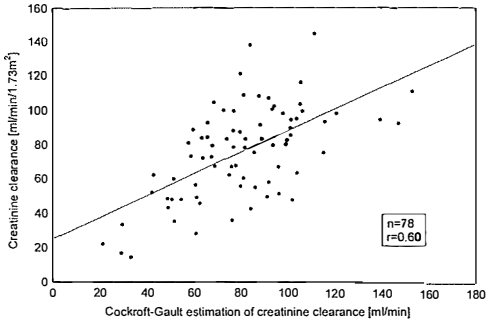

Figure 2. Correlation between creatinine clearance and Cockroft-Gault estimation of creatinine clearance in 47 patients and 78 simultaneous determinations.

(sensitivity) by CrCo was statistically significantly better than HC (p= 0.03) and serum creatinine concentration. There were no differences in the prediction of CrCl ≥78 ml/min/m^2 (specificity) between CrCo and HC (p=0.3).

Discussion

The present study, comprising 47 cancer patients in whom 78 simultaneous measurements of serum creatinine concentration, CrCl, HC and estimation of CrCl using Cockroft and Gault formula, indicates that the serum creatinine concentration, HC and CrCo cannot be used for early detection of renal insufficiency instead of CrCl.

The sensitivity of serum creatinine concentration to estimate CrCl < 78 mL/min /1.73m^2 was 41%. The poor sensitivity of creatinine in detecting CrCl < 78 mL/min /1.73m^2 may be due to a variety of renal and non-renal influences on the creatinine concentration. It is well established that the serum creatinine concentration is influenced by protein intake, the muscle mass, age, gender, race and drugs like cimetidine interfere with tubular secretion of creatinine.[4,9] The coefficient of day-to-day variations in creatinine excretion ranges between 3% to 14%, and may be as high as 70% when 24-hour urine collection errors are not eliminated.[8,9] Part of this variation arises from daily variation of GFR, which is variously reported to

have a coefficient of variation of 11% or even 17%.[8,9]

To account for differences between individuals in creatinine production, creatinine clearance can be obtained. However, estimation of GFR by CrCl is usualy overestimated for 10 to 40% due to errors during the 24-hour urine collection and to the tubular secretion of creatinine.[5] The ratio of CrCl to GFR was almost always greater and increased with decreasing GFR to a maximum of approximately 1.7 at a GFR of approximately 20 ml/min.[9,17] However, several reports have also shown that, in conditions where GFR is moderately impaired or normal and urine collection errors are reduced substantially by technicians who are trained to measure the urine volume and times of voiding, the CrCl is just about equal to GFR with a ratio of CrCl and GFR of approximately 1.15.[7,17,18] In this study, GFR was estimated by CrCl at a high accuracy rate because a majority of patients had mild to moderate impairment in renal function and, in order to minimize error in 24-hour urine collection, all patients were hospitalized and carefully monitored by trained technicians.

The estimation of GFR from the serum creatinine concentration, using Cockcroft and Gault formula usually overestimates GFR.[10] In our study, CrCo overstimated CrCl in 32% cases. This overestimation may be partly explained by day-to-day variability of creatinine metabolism and overweight of majority of study participants. Their mean body weight was 73 kg and mean body mass index was higher than 26 kg/m^2. Among obese patients, serious errors arise in the Cockcroft and Gault equation. It has been therefore suggested that among obese patients the Cockcroft and Gault equation should take account of lean body weight.[19,20] So, the standarization of the equation for body size is important for an appropriate comparison with a measure of GFR that is standarized similarly.[11] Due to the overestimation of GFR and great variability using of Cockcroft and Gault equation was not recomanded in the patients with advanced renal failure. Toto et al[10] found less variability in predicting GFR from the serum concentration of creatinine alone than from Cockcroft and Gault equatation in the subjects with creatinine values ranging from the upper limit of normal to 400 μmol/L. Several studies have shown that, in the patients with normal or a mild to moderate decrease in renal function, despite substantial errors in 24-hour urine collection and variability of creatinine metabolism and GFR, the estimation of CrCl using Cockcroft and Gault formula is less precise for GFR than CrCl.[9,11,17] The sensitivity of CrCo to predict reduced CrCl was 68%. However, the prediction of CrCl < 78mL/min/m^2 by CrCo was significantly better than prediction by serum creatinine concentration.

We found out that the estimation of GFR by HC overestimated CrCl in 54% of cases.

The sensitivity of HC in the estimation of reduced GFR was 46% only and was hardly any better than that of creatinine serum concentration (41%), whereas the specificity of serum creatinine concentration was considerably better. GFR depends upon the renal plasma flow and filtration fraction. In normal conditions, 20% of the blood plasma entering the kidneys is filtrated within the kidney.[20] As HC is an important measure of renal circulation, the GFR estimation can hardly be reliable with regard to plasma flow irrespective to the variability of filtration fractions. Our results are in accordance with the results of Chachati and coworkers,[16] who found that despite fair correlation between uptake of ^{131}I-hippuran clearance estimation and PAH clearance, the variability of HC was too large.

Renography is by far the best method for the early recognition of renal tubular disorders. In patients with early detected intrarenal and extrarenal secretion disorders by radioisotope renography and normal GFR dose modification of CDDP is not required. It

is generally known that mild secretion disorders, though impairing GFR, do not considerably increase the CDDP toxicity. Therefore, this method is as harmless in the patiens with one kidney only as in the patients with both kidneys because CDDP does not induce any serious renal failure at a normal level of CrCl.[1]

To prevent acute and chronic renal injury by CDDP, despite aggressive and careful hydration, the dose of CDDP must be modified according to GFR which provides the best overall measure of renal function. In general, the dose of CDDP in GFR 30 to 60 ml/min has to be lowered by half, whereas at a GFR lower than 10 or 30 ml/min the treatment with CDDP should to be discontinued.[1,2] Our results indicate that the serum creatinine concentration, estimation of CrCl by CrCo and estimation HC cannot equivalently replace CrCl as the best estimation of GFR before chemotherapy.

Conclusions

In patients with normal or moderately reduced renal function, the CrCl is more informative than serum creatinine concentration, CrCo and/or HC. Low sensitivity and specificity of this methods cannot provide a good screening test for early renal failure and cannot substitute the CrCl in the estimation of GFR. The estimation of renal function before chemotherapy by CrCo and HC is therefore unnecessary and inconvenient; moreover, serious damage to patients can be induced by considering their normal values before chemotherapy.

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