ESTIMATION OF CREATININE CLEARANCE IN PATIENTS WITH UNSTABLE RENAL FUNCTION, WITHOUT A URINE SPECIMEN.

Roger Jelliffe, M.D.

Laboratory of Applied Pharmacokinetics,
Division of Geriatric Medicine,

USC Keck School of Medicine,

2250 Alcazar Street, Los Angeles CA 90033

Phone 323-442-1300
Fax 323-442-1302
Email jelliffe@hsc.usc.edu

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Abstract

Background: There is a significant need to estimate creatinine clearance easily in acutely ill patients with unstable renal function, who have rapidly changing serum creatinine values and who need careful individualization of drug dosage, all without the problems associated with having to collect the traditional carefully timed urine specimen. **Method**: The daily change in the total amount of creatinine is the difference between its production and excretion. Production is estimated based on studies by others, using many carefully timed urine specimens. Daily creatinine production is related both to age and to the serum creatinine concentration. Urinary excretion of creatinine is equal to creatinine clearance times the average of a pair of timed serum creatinine concentrations, times the duration of the collection (usually 24 hours). **Results**: Good correlation was found between conventional measured creatinine clearances and the estimated values. The estimates had a precision essentially equal to that of the traditional method. **Conclusions**: One can now estimate the creatinine clearance which makes serum creatinine change from an initial concentration at one stated time to another concentration at another stated time, for a patient of a stated age, gender, height, and weight, without requiring a urine specimen. This method has been incorporated into software to perform the calculations easily and rapidly, and has been integrated into the USC*PACK PC programs for planning, monitoring, and adjusting individualized dosage regimens of drugs.

Introduction

Especially for purposes of providing guidance for dosage of renally excreted drugs that are potentially toxic, estimation of creatinine clearance (CCr) has long been a problem in acutely ill and unstable patients, largely because of difficulty in collecting the traditional carefully timed urine specimen in such patients. A number of years ago, several methods were developed to estimate CCr without a urine specimen [1-4]. However, those approaches only considered the situation where serum creatinine was stable. To overcome this problem, a dynamic approach to the problem was developed.

A Dynamic Model of Creatinine Kinetics

The dynamic model [5] first used the relationship that the daily change in the total amount of creatinine in a patient's body is the difference between creatinine production (P) and excretion (E) during that day. This was described by

$$V(C_2-C_1) = P - E \qquad (1)$$

where V is the apparent volume of distribution of serum creatinine (in hundreds of ml), C_1 and C_2 are the first and second serum creatinine values taken typically one day apart (in mg/dL), and P and E are production and excretion in mg. Since V is somewhat less than total body water, it was empirically approximated as 40 % of the patient's total body weight (in hundreds of grams).

Calculation of Daily Creatinine Production

The Effect of Age.

The data of Siersbaek-Nielsen et al. [2] of the effect of age upon the carefully measured 24 hour urinary creatinine excretion, in hospitalized patients who were clinically free of any renal disease, was shown to be described by

$$E = 29.305 - 0.203A \qquad (2)$$

where E is the measured urinary creatinine excretion (in mg/kg/day) and A is the age (in years). Since the patients were all quite stable, and in a steady state,

$$E = production. \qquad (3)$$

In this way, one can use this carefully measured data of excretion to estimate daily creatinine production, adjusted for the patient's age. This estimate can be further refined as described below. It should also be noted that in these patients, their average serum creatinine concentration, in almost all age groups, was 1.1 mg/dL [2]. This will be useful below.

The Effect of Serum Creatinine.

It was shown by Goldman [6] that uremic patients also have a decreased excretion (and therefore production) of creatinine. Using data from that report, creatinine production ($P_{Goldman}$, in mg /day for an average size patient) is related to serum creatinine (C, in mg/dL) by

$$P_{Goldman} = 1344.4 - 43.76C \tag{4}$$

Based on this, one can now adjust the estimate of creatinine excretion (and therefore production) for age as given in Eqn (2), and now to the average value (C_{avg}) of the patient's C_1 and C_2 by the ratio R, where

$$P_1 = 1344.4 - 43.76 \times C_{avg}, \tag{5}$$

and

$$P_2 = 1344.4 - 43.76 \times 1.1, \tag{6}$$

where 1.1 = the average serum creatinine in Siersbaek-Nielsen's patients, in each age group, as described above. Then,

$$R = P_1 / P_2, \text{ and} \tag{7}$$

the adjusted creatinine production, or $P_{adj} = E \times R$ \hfill (8)

In our original work [5], the best empirical correlation between measured and estimated CCr was finally found by taking 95% of P_{adj}, and then by taking a further 15% reduction of that. In that way, daily creatinine production could be estimated for men, based on many careful measurements of 24 hour urinary creatinine excretion, and adjusted to the patient's age, weight, and serum creatinine concentration [6]. In further adjustments, 90% of the value for men was then taken if the patient was female.. This gave the best correlations between estimated and measured CCr when renal function was severely impaired.

However, the above 15% reduction led to biased underestimations of about 15 % when renal function was close to normal [5]. Because of this, we have now modified the original algorithm to apply the above 15 % reduction only to patients who are on hemodialysis or

peritoneal dialysis. Removal of the 15 % restriction now results in the improved estimates for nondialysis patients, as shown in Figure 1, which are less biased than those found with the previous procedure [5]. This removal is reasonable because at the time of the transplant, the patients' serum creatinine concentration began to fall, and they ceased to be dialysis patients any more, as their renal function improved to clearances that finally were quite close to the normal range.

Further, if a patient's muscle mass is clearly above or below normal, as may be the case with very muscular patients, or conversely in cirrhotic patients, those with AIDS, or very obese patients, for example, one can make a rough clinical estimate of the patient's body (muscle) mass as perceived on physical examination as a percent of normal, if desired, to make a further final adjustment of P. There are no specific rules for this – only that one can make a rough clinical estimate. This adjustment for muscle mass was not done either in the original study [5] or in the present one. However, it provides an additional clinical degree of freedom to protect against overestimation of CCr in cachectic or very obese patients, or underestimation of it in very muscular patients. The range currently permitted in these estimates is from 70 to 130 percent of normal.

Calculation of Daily Creatinine Excretion

In the traditional calculation of creatinine clearance,

$$C = UV/P, \tag{9}$$

where U is the urinary creatinine concentration, V is the 24 hour urine volume, P now is the plasma or serum creatinine concentration, and C is creatinine clearance. This can be rearranged to show that what comes out of the body is equal to what was cleared from the body. Thus

$$PC = UV. \tag{10}$$

Because they are numerically equal, PC can therefore be substituted for UV, the measured 24 hour excretion. Thus

$$E = UV = PC, \text{ and}$$

$$E = C_{avg} \times CCr \times 1440, \hspace{3cm} (11)$$

where E is expressed in total mg/day, C_{avg} is the average of the two serum creatinine concentrations, in mg/dL, CCr is in hundreds of ml/min, and 1440 represents the number of minutes in one day.

The Final Overall Algorithm

The final overall algorithm to calculate creatinine clearance from unstable serum creatinine values, and without requiring a urine specimen, may now be written as

$$0.4W(C_2 - C_1)/T = P_{adj} - C_{avg} \times CCr \times 1440 \hspace{2cm} (12)$$

Where W is body weight in hundreds of grams, C_1 and C_2 are the first and second serum creatinine values in mg/dL, T is the time in days between the two serum creatinine samples, C_{avg} is $(C_1 + C_2)/2$, CCr again is in hundreds of ml per minute, and 1440 is the minutes in one day. One can then rearrange the equation and solve it for CCr. After this, the raw creatinine clearance above can be corrected for body surface area to that of an average patient having a body surface area of 1.73 square meters.

The above equation thus represents a dynamic model of creatinine kinetics, and permits estimation of CCr from routine clinical data of age, gender, height, weight, and either a pair of unstable and changing serum creatinine levels or a single stable serum creatinine, all without having to collect a urine specimen, which usually is a difficult and unreliable procedure in all but research situations, especially for unstable and acutely ill patients, who are often in intensive care units.

Comparison of Estimated with Measured Creatinine Clearance

In a first set of 128 observations on an initial group of 15 patients who had just undergone renal transplantation in the renal transplant unit of the Los Angeles County – USC Medical Center [5], the algorithm was shown to have an accuracy essentially equal to that of Jadrny [1]. Those 15 patients consisted of 9 men and 6 women. Their age averaged 44.1 years, and ranged from 21 to 70 years. Body weight averaged 135.5 lb, and ranged from 105 to 202 lb. The number of serum creatinine samples obtained from each patient averaged 8.5, and ranged from 1 to 25.

In an additional set of 250 observations on a second group of 14 similar patients who also had just undergone renal transplantation, the standard error of the estimate (±14.9 ml/min) was slightly more precise that the equations of Jadrny (±16.6 ml/min), with an overall scatter of about ± 25% between the estimated and the measured values, as shown in Figure 1. In these 14 patients, 8 men and 6 women, their age averaged 36 years, and ranged from 22 to 55 years. Body weight averaged 144 lb, and ranged from 101 to 190 lb. The average number of serum creatinine samples per patient was 16.8.

Errors in the traditional estimation of Creatinine Clearance

As a control, one must consider the errors present in the traditional determination of CCr. If one can measure a serum creatinine concentration with a coefficient of variation of 5%, as is the case with many common autoanalyzer methods, and if one measures urinary creatinine concentrations with a coefficient of variation of 8%, as is also common, then if one can collect a 24 hour urine specimen with a coefficient of variation of 5%, these errors will propagate so that the resulting value of the traditionally measured creatinine clearance will have a coefficient of variation of 11%. The resulting 95% confidence limit is therefore ± 22%. This error closely corresponds to the scatter found between the estimated and measured CCr values shown in Figure 1. Because of this, it is likely that the present method of estimating CCr without a urine specimen has a precision approximately equal to the classical measurement of creatinine clearance. It addition, it is practical in clinical situations. It is probably better at sensing rapid changes in renal function in response to sudden changes in serum creatinine than are the more simple formulas of Jadrny [1], Jelliffe [3], or Cockcroft and Gault [4], which were designed only for use when serum creatinine is stable, as serum creatinine usually requires about one week to stabilize following a change in renal function.

Table 1 shows a comparison of the present method with that of Cockroft and Gault [4] when serum creatinine is stable. Table 2 shows the effect of a rise or fall in serum creatinine over a 1 day period upon the estimated creatinine clearance, for a 50 year old male with a body surface area of 1.73 square meters.

The Question of Ideal Body Weight

It would seem logical to correct the estimate of creatinine production and muscle mass by using some estimate of ideal body weight. However, in anecdotal examinations of this question in several morbidly obese patients, somewhat more precise estimates of CCr were actually obtained using total body weight than by using various estimates of ideal body weight. Because of this, we have continued to use total body weight in preference to an estimate of ideal body weight. The clinical estimation of muscle mass as a percent of normal is a useful option here. It would be interesting to study this question further in another study.

Conclusion

The method described here for estimating CCr in acutely ill and unstable patients provides a useful tool for evaluation of a patient's renal function in a practical manner when serum creatinine concentrations are unstable, changing from day to day. It is especially useful in that it permits linkage of this information about rapid relative changes in a patient's renal function to evaluate the pharmacokinetic and dynamic behavior of drugs in such patients, thus permitting improved understanding and tracking of drug behavior, and improved individualization of drug dosage regimens, in such patients.

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Table 1. Comparison of the present method (J) with that of Cockroft and Gault (CG) [4]. Figures are in ml/min/1.73 M^2 for the present method, (J), and in ml/min for Cockcroft and Gault (CG), for a 72 kg patient. Values are given as J/CG for serum creatinines from 0.6 through 3.0 mg/dL, and as J-nondialysis patient/J-dialysis patient/CG for serum creatinines of 5.0 and 10.0 mg/dL.

Creatinine clearance estimate

SCr	Male (J/CG)			Female (J/CG)		
	20yrs	50 yrs	80 yrs	20 yrs	50 yrs	80 yrs
0.6	198/200	150/150	102/100	178/170	135/128	92.0/85.0
1.0	117/120	88.7/90.0	60.5/60.0	105/102	79.9/76.5	54.5/51.0
3.0	36.4/40.0	27.6/30.0	18.8/20.0	32.7/34.0	24.8/25.5	16.9/17.0
5.0	20.2/17.1/24.0	15.4/13.0/18.0	10.5/8.9/12.0	18.2/15.4/20.4	13.8/11.7/15.3	9.4/8.0/10.2
10.0	8.2/6.9/12.0	6.2/5.2/9.0	4.2/3.6/6.0	7.3/6.2/10.2.	5.8/4.7/7.7	3.8/3.2/5.1

Table 2. Effect of rise and fall of serum creatinine in one day on estimated creatinine clearance.

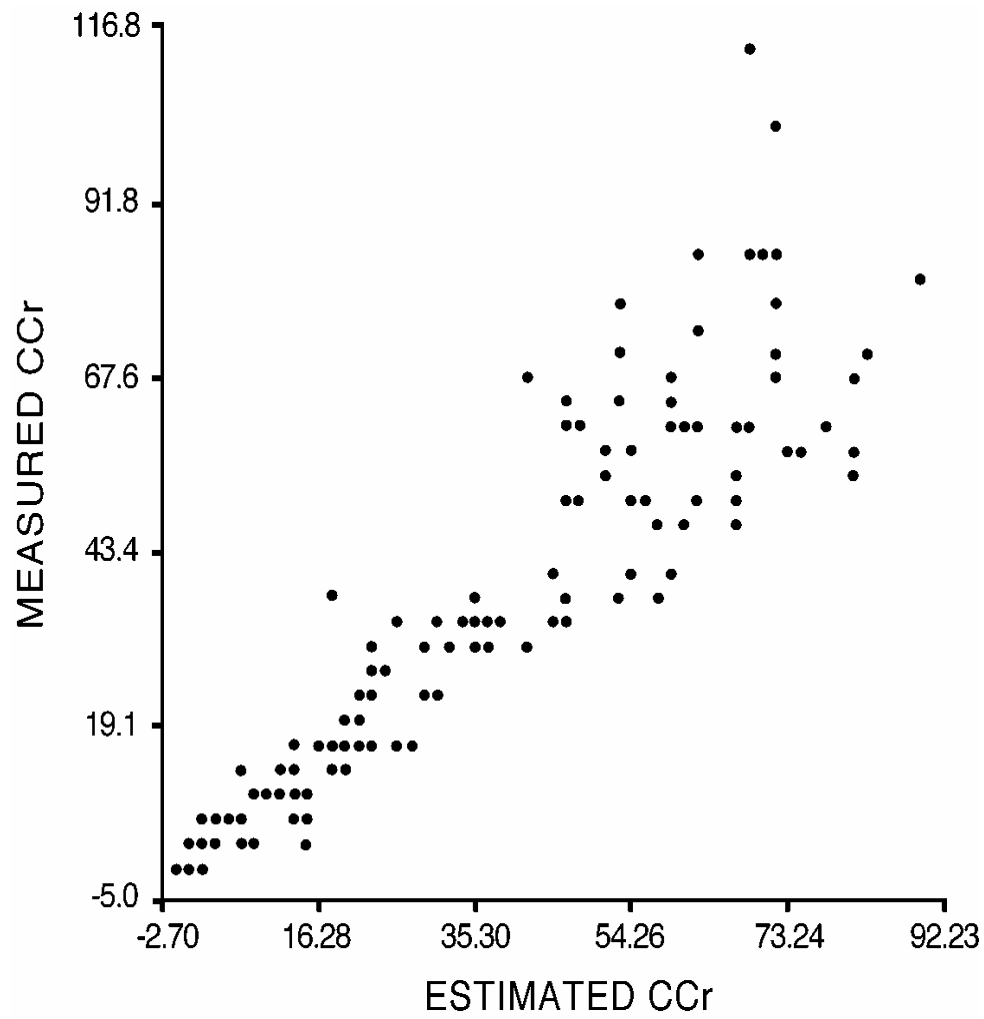| First sample (mg/dL)	Second sample (mg/dL)	Est CCr (ml/min/1.73m2
.6	0.6	150
.6	1.0	102
.6	3.0	22
.6	5.0	0.0
1.0	0.6	121
1.0	1.0	89
1.0	3.0	23
1.0	5.0	1.7
3.0	0.6	74
3.0	1.0	62
3.0	3.0	28
3.0	5.0	10
5.0	0.6	60
5.0	1.0	54
5.0	3.0	30
5.0	5.0	15

Figure legend

Figure 1. Comparison of Estimated CCr as described herein, with measured CCr.

Figure 1. Comparison of Estimated CCr as described herein, with measured CCr.