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The description of a method for accurately estimating creatinine clearance in acute kidney injury

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ABSTRACT

Background: Acute kidney injury (AKI) is a common and serious condition encountered in hospitalized patients. The severity of kidney injury is defined by the RIFLE, AKIN, and KDIGO criteria which attempt to establish the degree of renal impairment. The KDIGO guidelines state that the creatinine clearance should be measured whenever possible in AKI and that the serum creatinine concentration and creatinine clearance remain the best clinical indicators of renal function. Neither the RIFLE, AKIN, nor KDIGO criteria estimate actual creatinine clearance. Furthermore there are no accepted methods for accurately estimating creatinine clearance (K) in AKI.

Study design: The present study describes a unique method for estimating K in AKI using urine creatinine excretion over an established time interval (E), an estimate of creatinine production over the same time interval (P), and the estimated static glomerular filtration rate (sGFR), at time zero, utilizing the CKD-EPI formula. Using these variables estimated creatinine clearance (Ke) = E/P * sGFR.

Setting and participants: The method was tested for validity using simulated patients where actual creatinine clearance (Ka) was compared to Ke in several patients, both male and female, and of various ages, body weights, and degrees of renal impairment. These measurements were made at several serum creatinine concentrations in an attempt to determine the accuracy of this method in the non-steady state. In addition E/P and Ke was calculated in hospitalized patients, with AKI, and seen in nephrology consultation by the author. In these patients the accuracy of the method was determined by looking at the following metrics; $E/P > 1$, $E/P < 1$, $E = P$ in an attempt to predict progressive azotemia, recovering azotemia, or stabilization in the level of azotemia respectively. In addition it was determined whether $Ke < 10$ ml/min agreed with Ka and whether patients with AKI on renal replacement therapy could safely terminate dialysis if Ke was greater than 5 ml/min.

Outcomes and results: In the simulated patients there were 96 measurements in six different patients where Ka was compared to Ke. The estimated proportion of Ke within 30% of Ka was 0.907 with 95% exact binomial proportion confidence limits. The predictive accuracy of E/P in the study patients was also reported as a proportion and the associated 95% confidence limits: 0.848 (0.800, 0.896) for $E/P < 1$; 0.939 (0.904, 0.974) for $E/P > 1$ and 0.907 (0.841, 0.973) for $0.9 < E/P < 1.1$. $Ke < 10$ ml/min correlated very well with Ka, while $Ke > 5$ ml/min accurately predicted the ability to terminate renal replacement therapy in AKI.

Limitations: Include the need to measure urine volume accurately. Furthermore the precision of the method requires accurate estimates of sGFR, while a reasonable measure of P is crucial to estimating Ke.

Conclusions: The present study provides the practitioner with a new tool to estimate real time K in AKI with enough precision to predict the severity of the renal injury, including progression, stabilization, or improvement in azotemia. It is the author's belief that this simple method improves on RIFLE, AKIN, and KDIGO for estimating the degree of renal impairment in AKI and allows a more accurate estimate of K in AKI.

Abbreviations: AKI, acute kidney injury; GFR, glomerular filtration rate; K, creatinine clearance; Ka, actual K; Ke, estimated K; Ks, static K; C, serum creatinine concentration; U, urine creatinine concentration; E, creatinine excretion; P, creatinine production; Vd, creatinine distribution volume.

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1. Introduction

Acute kidney injury (AKI) is a common and serious medical condition encountered in hospitalized patients. When present it contributes significantly to morbidity, mortality, and overall health care costs due to the derangements in fluid, electrolyte, and acid base balance which further complicate the course of an illness and increase the challenge of managing these often devastating metabolic consequences [1–13].

The most recent classifications estimate the degree of renal impairment using the Risk, Injury, Failure, Loss, End stage renal disease (RIFLE), Acute Kidney Injury Network (AKIN) and The Kidney Disease Improving Global Outcomes (KDIGO) criteria. These methods attempt to estimate the degree of kidney injury using a measure of absolute or relative rise in serum creatinine concentration or determining the duration of oliguria [2,9–12]. Shortcomings to these criteria include the fact that neither method estimates actual glomerular filtration rate (GFR) or creatinine clearance (K) and hence infer the extent of renal injury. Furthermore, by relying on serum creatinine concentration (C) and changes in C (dC/dt), there are inherent errors related to different creatinine kinetics which vary between patients, based on muscle mass, making direct correlations between patients unreliable. Additionally, there are situations where significant falls in GFR are not detected due to a delay in the rise in C. There are also dilution effects of parenteral solutions on C and dC/dt. It is for these reasons that AKIN, RIFLE, KDIGO or other methods which rely on C are not reliable metrics for accurately measuring GFR or K in AKI. Finally, the estimate of renal injury is made retrospectively and does not allow one to predict the course of the renal impairment prospectively [14–21].

Regardless of the method used to establish the diagnosis of AKI, KDIGO states that the serum creatinine concentration (C) and creatinine clearance (K) remain the single best markers of kidney function and should be measured whenever possible [2,22–25]. Formulas to measure K in AKI have been described [26–29] and are equations based on creatinine mass balance in the non-steady state (S appendix). Although mathematically accurate they are not ideal for clinical use due to the fact they require an accurate value for creatinine distribution volume (Vd), as well as a measure of changing creatinine concentration (dC/dt). These values are difficult to measure precisely and are prone to large errors related to parenteral fluid administration and dilution of the value for Vd and dC/dt, rendering these methods impractical for clinical use [20,21].

This paper describes a method relying on principals of creatinine mass balance and K estimation using the urine creatinine excretion (E) as opposed to serum creatinine (C). This method is more accurate than those relying on serum creatinine in that urine creatinine concentration (U) and urine volume (V) are measured directly and accurately, and not estimated, while the term static K (Ks) is introduced and represents the creatinine clearance as determined by CKD-EPI, at any time zero in the course of AKI.

2. Methods

2.1. Description of formula

In the steady state creatinine production (P) is equal to renal creatinine excretion (E). In such cases the serum creatinine concentration is constant with $K = U*V/C$, where K is inversely proportional to C [16,24,29,30]. Furthermore the steady state allows one to estimate GFR by using estimating formulas such as MDRD or CKD-EPI. From this one can appreciate that when E is less than P, C will rise and the patient is in AKI. When E is greater than P, C is falling and the patient is recovering from AKI. When E is zero, K is zero. Finally, when E = P, a steady state is reached and may represent normalization of renal function or a plateau has been reached in the course of AKI where C is stable [21].

Fig. 1 shows the simulation of a patient with AKI with a sudden drop in K from 100 ml/min to 10 ml/ min. This is associated with an abrupt fall in E followed by a steady rise until E = P and a new steady state has been reached reflecting the actual K of 10 ml/min. The slope of dC/dt is positive reflecting the net accumulation of creatinine in the serum. At each time interval, the area An represents the net serum accumulation of creatinine, which is equal to $Vd * (C2 - C1)$ where Vd is the distribution volume for creatinine (Fig. 2). Moving from left to right across the x axis in Fig. 1, as each area An falls, there is a reciprocal rise in E, while the ratio E/P rises until finally C peaks at the level that corresponds to the actual K, which in this example equals 10 ml/min. At this point in time a new steady state has been reached, where An = 0, as C is no longer rising, E = P, and K can be estimated directly or measured.

In Fig. 2 one sees that E = P – An (where $An = Vd * (C2 - C1)$. Rearranging we find that $E/P = 1 - An/P$. When An is large, E/P is small and GFR is low. When An is small, E/P approaches one and a plateau is being reached. When An is zero, E = P. This represents the plateau and is the only time when K can be estimated or measured in AKI by standard methods.

From this one can appreciate that when: $E/P < 1$, the patient is in AKI, $E/P > 1$ the patient is in a recovery pattern, $E/P = 1$ a plateau has been reached and GFR can be estimated or measured, and finally when $E/P = 0$, K is zero.

Referring again to Fig. 1 the method can be developed further. At any point in the graph between the onset of renal injury and the plateau there is progressive fall in estimated K by CKD-EPI or MDRD corresponding to each changing value for C. Each measure for K would only be valid if E was equal to P from that corresponding time going forward. The level for estimated K at any point in time is called static K (Ks) and represents the actual K if indeed one was in a steady state. With each corresponding time interval, from onset of injury to plateau, there is a progressive fall in the value for Ks accompanied by a proportional rise in E/P so that, at any time interval, the product of Ks at time 0 and E/P at time 0 to time 1 is a constant and is in fact equal to Ke.

The final formula states that; $Ke = Ks * E/P$ at any time interval t0 to t1, where Ks equals K at t0 by CKD-EPI, E is measured directly as U*V over the same time interval, and P is estimated by the following formulas as described by Bjornsson; P (male) = $(27 - .173 * \text{age}) * \text{weight in kg}$, and P (female) = $(25 - .175 * \text{age}) * \text{weight in kg}$ over 24 h [11]. Where weight is lean body weight and P falls by 2% for each hospital day [21].

2.2. Simulated patients

To prove that the formula $Ke = Ks*E/P$ was valid involved a more detailed analysis of the mathematics of creatinine kinetics in AKI. Beginning with the basic formula for creatinine clearance in AKI, where $dC/dt = P/V - C*K/V$. The integral of this formula solves for C with respect to t, where $C(t) = P/K + [C(0) - P/K]*e^{\wedge} - Kt/V$ [16,28 and Fig. 1].

Six different patients were simulated (Tables 1–6) including variables of baseline renal function and renal function after AKI (Ka), body weight, age, and gender. V was estimated as 60% of body weight corresponding to total body water as an estimate of creatinine distribution volume [29], P was estimated by the method described above, and C, at time zero, was directly calculated from the equation K = P/C in the steady state. For each patient $V*dC/dt$ was calculated at several time intervals, and was equal to V [C(t) – C(0)] divided by the time interval, which represents the