Short Communication

Describing a Simple and Accurate Method for Measuring 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 in AKI. The present study describes a new, unique, and simple 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. Patient examples are provided to highlight the use of this method and its advantage over AKIN, RIFLE, or KDIGO which have the above mentioned shortcomings while often incorrectly classifying the extent of renal injury in the patient with 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

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 [1,2]. 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 [1,3-12]. 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 [13].

Regardless of the method used to establish the diagnosis of AKI, KDIGO guidelines for AKI state that the serum creatinine concentration (C) and creatinine clearance (K) remain the single best markers of kidney function and should be measured whenever possible (3). Formulas to measure K in AKI have been described [14-18] and are equations based on creatinine mass balance in the non-steady state. 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.

A real time, easy to perform, reliable and accurate estimate of GFR or K has been an elusive missing metric in AKI. Its usefulness in clinical medicine is clear in that one would have an accurate measure of renal injury, where the course and severity can be predicted in advance. Furthermore one could anticipate a plateau phase followed by a recovery which may also be anticipated well in advance of a changing C. A method to accurately estimate G or K, real time, is a welcome and overdue tool in the study of AKI.

The author recently published a paper which describes a method for estimating K in AKI, 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. Details of the method are described in reference 1 and the Appendix. Figure 1 provides an example of the pattern of creatinine excretion in AKI and the logic behind the method for measuring K in AKI, where Ke = Ks x E/P. In this method E is directly measured using a four, six or eight hour urine sample. P is estimated by the following formulas; P (male) = (27-.173 * age)* weight in kg, and P (female) = (25-.175 * age)* weight in kg over 24 hours. Where weight is lean body weight and P falls by 2% for each hospital day [19].

Furthermore it was shown that the E/P ratio prospectively predicts the direction of azotemia where; E/P < 1 predicts a rising C, E/P > 1 predicts a falling C, and E=P predicts a stable C [19,20].

Based on this background it is apparent that by taking the product E/P and Ks at any time t0, we incorporate into our calculation a value for baseline K, whereupon the value of Ke is a reflection of Ks and directly affected by the ratio E/P. Hence, when E/P <1, Ke < Ks. When E/P >1, Ke > Ks. When E=P, Ke = Ks, with the actual value for Ke equal to Ks*E/P.

The significance of this method is demonstrated by the following examples;

Example 1

In the case of two patients with a urine output of 500 ml in twenty fours, the same value for C at the time tested, and an identical estimation for P, the patient with the greater value for E will have a less severe renal injury for any level of Ks. In a similar way these same two patients with an E/P value of .5 will have very different values for Ke if in one case the Ks at t0 is 100 ml/min and in the other 40 ml/min where the value for Ke in these patients will be 50 ml/min and 20 ml/min respectively. One can appreciate that E/P determines the direction of the azotemia and Ks provides a baseline value used to determine Ke.In both cases AKIN and RIFLE would be inaccurate and misleading as to the extent of renal injury.

Example 2

A patient with CKD and a baseline C of 4 mg/dl presents with bladder outlet obstruction and a C of 8.7 mg/dl. The bladder is decompressed, the urine output is brisk. The E/P ratio is .7, Ke is 5 ml/min. This suggests lack of recovery with relief of the obstruction, progressive azotemia ensues, and renal replacement therapy is initiated.

Example 3

A patient presents with sepsis and shock. On presentation he is resuscitated with crystalloid and given antibiotics. C is 1.5 mg/dl, the urine output is less than 500 ml in the first 24 hours. E/P
is .6. Ke is 25 ml/min suggesting the patient will not need renal replacement therapy. C peaks at 2.94 mg/dl and then gradually declines.

Example 4
A patient presents with acute pancreatitis with a C 3.2 mg/dl. He is resuscitated with crystalloid and colloid. The E/P ratio is .18, and Ke 4 ml/min. Renal replacement therapy is initiated on day 4 with a C level of 5.65. On day 28 the urine output was noted to steadily rise, exceeding 2000 ml per day. It is on day 35 that Ke has risen to 10 ml/min and dialysis is safely terminated with gradual renal recovery noted.

Example 5
An elderly patient presents with signs of hypovolemia. He is resuscitated with isotonic crystalloid. On day 1 C is 1.45 mg/dl. The patient is oliguric and on day 2 it has risen to 3.81 mg/dl. The E/P ratio is 2.7, Ke is 43 ml/min predicting rapid renal recovery. On days three and four C falls to 2.55 and 1.63 respectively consistent with rapid improvement in K as reflected by the favorable E/P ratio and Ke.

Example 6
A middle aged man with alcoholic hepatitis presents with hepatic decompensation. On day one C is .68 mg/dl. By day 4 C has risen to 3.35 mg/dl, E/P is less than .1, and Ke is essentially zero. On day five RRT is initiated due to progressive azotemia and symptomatic fluid excess. On day 25 C is 3.57 mg/dl, E/P ratio is .67, and Ke is 10 ml/min despite persistent oliguria. This suggests that C will continue to rise in the short term and renal function has begun to recover. As predicted C rises and peaks at 5.1 mg/dl on day 27. On day 30 the patient remains oliguric yet E/P is now 1.3 and Ke is 30. This is followed by a gradually falling C as predicted by these last measurements.

Example 7
A young patient with CKD due to chronic glomerulonephritis and a baseline C of 2 mg/dl presents with superimposed pre-eclampsia with C 2.45 ml/dl on day 1. She undergoes emergency C section. On day 3 C has risen to 2.81 mg/dl, E/P is .86, and Ke is 20 ml/min. Using the steady state formula for K = P/C, solving for C gives a value of 4.2 mg/dl which reflects the peak C value when E/P = 1 and K can be calculated directly. In this case the patient’s actual peak C was 4.1 mg/dl followed by a gradually falling C.

Example 8
An elderly patient presents with a massive pulmonary embolism with hypotension. He is treated with pressors, crystalloid and anticoagulants. On day 1 C is .81 mg/dl. On day 3 C has risen to 2.31, the patient is oliguric, the E/P ratio is .3, Ke is 10 ml/min and C continues to rise as predicted. The patient is given high dose loop diuretic and responds with a brisk diuresis. Repeat testing reveals an E/P ratio of .25, Ke of 6 ml/min. Despite the presence of a diuresis these results suggest progressive renal injury as reflected by a continued rising C.

Example 9
An elderly patient with CKD and a baseline C of 2 mg/dl is hospitalized with pneumonia, sepsis, and respiratory failure. C on day 1 is 4.61 mg/dl and 4.63 mg/dl on day 2. The patient is mechanically ventilated, while receiving antibiotics, and pressors. The E/P ratio is 1.1 and Ke 16 ml/min. This predicts a gradual improvement if renal function reflected by a gradually falling C. Renal replacement therapy is not needed.

DISCUSSION
AKI is a common, serious, and often devastating disorder resulting in significant morbidity, increased risk of mortality, and excessive healthcare costs as a consequence of complications which may occur as a result [1,2]. It remains one of the most challenging disorders encountered in medicine often requiring complex knowledge of pathophysiology across several organ systems and medical subspecialties. In the analysis of a patient with AKI, the physician is faced with determining etiology, pathophysiology, extent of renal injury, and reversibility whenever possible [7,8,21]. To this end, the AKIN, RIFLE, and KDIGO criteria have been proposed as the best estimates of renal injury [1,3-12]. These criteria do not establish pathophysiology or reversibility. Rather, the extent of renal injury is estimated by an absolute or relative rise in C, the duration of oliguria, or the need for RRT without signs of renal recovery. Neither GFR nor K is actually measured. Shortcomings to these criteria include potential errors with C and dc/dt due to dilution effects as well as differences in muscle mass and creatinine kinetics from patient to patient. Furthermore these estimates of renal injury are retrospective and have little impact on forecasting the actual extent of renal injury or the course of the azotemia during an episode of AKI [22,23].

A real time, easy to perform, reliable, and accurate estimate of GFR or K remains an elusive missing metric in AKI. Its usefulness in clinical medicine is clear in that one would have an accurate measure of renal injury, where the course and severity can be predicted in advance. Furthermore one could anticipate a plateau phase followed by a recovery which may also be anticipated well in advance of a changing C. A method to accurately estimate GFR or K, real time, is a welcome and overdue tool in the study of AKI.

The method described in this paper measures E using a four, six, or eight hour timed urine specimen, P is estimated, and KS equals estimated GFR at time zero by any standard GFR estimating equation such as MDRD or CKD-EPI [24-28]. From this one can measure the E/P ratio and predict the direction of the azotemia prospectively, while Ke = KS x E/P and the extent of renal injury can be predicted with accuracy.

The examples given above highlight the utility of this method in estimating renal function at any time while showing that AKIN, RIFLE, and KDIGO, by being static indicators of renal function in a dynamic and non-steady state, often misrepresents the extent of renal injury. In examples 1,3,5,6, and 8 one sees situations where patients with normal or near normal serum C levels have low values for Ke showing that significant renal injury can be detected at an early stage. There is no other measure of renal function or injury that has been show to accomplish this with accuracy and predictability.

There are other examples where C is elevated but Ke is actually higher than anticipated in patients with a functional
and reversible cause for AKI as is seen in example 5. In this case AKIN, RIFLE, and KDIGO would overestimate the degree or renal impairment.

There are also examples where urine output does not predict renal function as in the case of renal function recovery in the patient who remains oliguric with a falling C, likely due to the presence of liver disease where creatinine is excreted in a small urine volume due to enhanced renal absorption of tubular ultrafiltrate as a consequence of the liver pathology, while E is rising due to renal function improvement as seen in example 6. In a different situation, as in example 4, one sees the onset of a brisk diuresis does not predict renal recovery in dialysis dependent AKI and that a rising E is associated with the onset of recovery.

These examples serve to highlight many of the shortcomings of AKIN, RIFLE, and KDIGO which are overcome by this real time, easy to perform method to accurately measure K in AKI.

CONCLUSION

The method described in this paper provides an accurate and easy to perform tool for estimating K in the patient with AKI. When E/P is less than 1 the patient is in AKI with C rising. When E/P is greater than one the patient is in a recovery pattern with C falling. The ratio of E/P reflects the severity of azotemia and the size of dC/dt. When E is equal to P the patient is in a steady state and K can be estimated or measured directly. Multiplying E/P by Ks at any time 0 provides a very good estimate of actual K, real time, in the patient with AKI.

REFERENCES

APPENDIX

E is equal to creatinine excreted over a timed interval of four, six, or eight hours and is measured in mg.

P over 24 hours is estimated by the following formulas:

P (male) = (27 - .173 x age) x ideal weight in kg
P (female) = (25 - .175 x age) x ideal weight in kg

There is a 2% fall in P for each hospital day. The final value for P depends on the urine collection duration, where total P is divided by three, four, or six for an eight, six, or four hour sample respectively.

Ks = Estimated GFR at time zero at the onset of the urine collection.

The final formula for K = E/P x Ks.