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RESEARCH ARTICLE

Urinary Sodium/Potassium Ratio in Acute Kidney Injury Accurately Differentiates Prerenal Azotemia from Acute Tubular Necrosis

Theodore Shankel, Stewart Shankel*

Redlands Community Hospital, Redlands, USA

Objective: To develop a more accurate, cost effective, non-invasive test to differentiate between pre-renal renal failure (PRA) and acute tubular necrosis (ATN) in acute kidney injury (AKI). **Methods**: Urine sodium/potassium (Na/K) ratios were compared with fractional excretion of sodium (FeNa) and renal failure index (RFI) as well as other commonly used indices to differentiate patients with PRA from ATN. Patients with a rise in serum creatinine > 0.5 mg/d identified from medical records for a six- to eighteen-month period, were reviewed and categorized either as PRA or ATN based on presenting findings, course in hospital or renal biopsy. All patients had urinary sodium and potassium, creatinine, and serum creatinine done. **Results**: The Na/K was < 1 in PRA and > 1 in ATN, correctly identifying all 42 cases of PRA and all 28 patients with ATN. The FeNa was >1 and misdiagnosed 9 of 42 patients with PRA and was >1 and correctly diagnosed all patients with ATN. The RFI was >1 and misdiagnosed 11 of 42 patients with PRA but was >1 and correctly diagnosed all patients with ATN. The BUN/creatinine ratio, urine sodium concentration and U/P creatinine ratio all had a very poor correlation with the correct diagnosis. **Conclusion**: The Na/K ratio correctly diagnosed all 42 cases of PRA and all 28 cases of ATN. It is easy to do, is cost effective, non-invasive, and is useful for following patients with PRA to see if and when they develop ATN.

Keywords: acute renal injury, prerenal azotemia, tubular necrosis

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Introduction

The differential diagnosis of acute kidney injury (AKI) has been of major interest for nephrologists and for all physicians caring for patients with acute medical problems for over 50 years. This is not just an academic exercise but has significant medical consequences specifically with regard to fluid balance and drug administration. The major problem in AKI is differentiating between a poor perfusion state identified as pre-renal azotemia (PRA) and acute tubular necrosis (ATN) which are the major etiologies of AKI. Acute glomerulonephritis in the adult is rare and has a rather classical urinary sediment and a much different clinical presentation. Urinary obstruction in adults can be reliably diagnosed with renal ultrasound done 24-48 hours post onset of obstruction. Most patients are anuric but some high grade obstructions may occasionally be polyuric. Acute interstitial nephritis (AIN) is much less common than ATN and must be distinguished from ATN using parameters other than renal electrolyte indices.

In an attempt to differentiate between PRA and ATN, in 1970 Bricker [1] proposed measuring the urine sodium. If the urine sodium was <20 mEq/l this was indicative of PRA and >40 mEq/l suggested ATN. Over the next 10 years multiple researchers proposed numerous methods of differentiating between PRA and ATN. These included changing the urine sodium concentrations to < 20 mEq/l for PRA and > 30 mEq/l for ATN [2], the renal failure index (RFI) defined as U_{Na} x P_{Cr}/U_{Cr} [3], calculating fractional excretion of Na (FeNa) [4], and finally the calculation of the fractional excretion urea (FEUN) [5].

All of the above methods have some overlap and lack specificity. Furthermore the more accurate RFI and FE_{Na} require blood samples and FE_{Na} requires the measurement of the serum and urine creatinine and a timed urine collection. The urine creatinine is notoriously inaccurate, due to problems with collections of urine even in catheterized patients, and increased tubular secretion of creatinine in renal failure [6].

In this paper we are proposing a new method of differentiating between PRA and ATN. This method does not require blood samples, rather, only the collection of the spot urine for determination of Na and K concentration. Because of its simplicity and low cost it can be used repeatedly to monitor PRA to determine if and when the patient may be developing ATN. Its sensitivity and specificity are 100%.

Methods

This study was approved by the Institutional Research Review Board (IRRB) and patient consents were waived since it was a retrospective study with only a chart review and no patient identity was revealed. Over 200 patient charts were reviewed over a six-month period at Loma Linda University Medical Center (LLUMC), and over an 18 month period at Redlands Community Hospital (RCH). The study was based on patient data from LLUMC and RCH laboratories. Patients with a rise in creatinine >0.5 mg/dl were evaluated for study. Exclusion criteria: patients who were catabolic, on steroids, malnourished, had a persistent

* Correspondence to: Stewart Shankel
E-mail: stewshankel@gmail.com

high fever, or had blood in the gastrointestinal (GI) tract causing a rise in the BUN and not in the serum creatinine, patients with obstructive uropathy, patients taking distal sodium blockers affecting K^+ secretion, patients on massive loads of HCO_3^-, patients with chronic renal failure, patients with a rise in BUN, but a rise in serum creatinine less than 0.5 mg/dl were excluded from study. Patients who did not have serum and urinary electrolytes done on the same day or had no urinary electrolytes done and had to be eliminated due to a lack of data, or patients with lack of data to support a diagnosis of either PRA or ATN were also excluded. Only patients with an acute rise in serum creatinine > 0.5 mg/dl were included in the study.

A total of 42 patients were determined to have PRA based on their clinical diagnosis and course in hospital. Their diagnoses were typical of most poor perfusion states; cirrhosis, hepatorenal syndrome, congestive heart failure, dehydration, or postoperative volume depleted states. The mean urine volume of these patients at the time of measurement of the urine Na/K ratio, the FE_{Na}, and RFI was 860 ml/day. The urine outputs varied from 22 ml/day to 3,475 ml/day. The higher urine volumes were seen in the early recovery phase of PRA when some of the patients were on loop diuretics. Monitoring the daily urine output in many of these patients with PRA was of little value, since many had severe liver disease and urine outputs stayed low as did those patients with severe congestive heart failure who did not survive. Those patients who survived and did well had urine outputs that varied from day to day. In this patient population, 53% were female and 47% male. In 22 of these patients, ages ranged from 36-84 years with a mean age of 63 years. Comorbidities included diabetes mellitus in 27%, alcoholism, 12%, hypothyroidism, 13%, COPD, 13%, and cancer, 13%.

The urinalyses on these patients were benign with occasional one plus protein and 2-5 rbc (red blood cells) and wbc (white blood cells) per hpf (high power field). Urinary electrolytes, sodium, potassium and chloride and urinary urea and creatinine were measured on a spot urine sample close to the time when the serum values were done.

The time to recovery in those patients that survived or did not develop ATN varied from 4 days to 18 days with a mean recovery time of greater than 8.5 days. The mean drop in serum creatinine was 1.34 mgs/dl. Fourteen of the 38 patients were either on furosemide or bumetanide with a mean urinary Na/K ratio of 0.29, which was slightly less than the 0.32 Na/K ratio in those patients who were not on diuretics (see Table I).

Twenty-eight of the patients were determined to have ATN based on their clinical presentation and course in hospital. Four had prolonged shock, seven had sepsis, one of whom received gentamycin. Four received IV contrast in the presence of, or prior to, liver failure, surgery for abdominal aortic aneurysm (AAA), and one had stage IV immunoblastic sarcoma. Two received nephrotoxic antibiotics and two had acute rhabdomyolysis, the remainder were due to SLE with anaphylactoid vasculitis secondary to penicillin (biopsy proven ATN), acute lymphocytic leukemia with ATN at post, multiple myeloma, post severe seizure disorder and post cerebral hemorrhage.

Urine volumes varied considerably depending on the severity of the kidney injury (polyuric or oliguric ATN). Some patients presented with ATN and others developed ATN in the hospital. Urine volumes at the time of study varied from a low of 10 ml/day to a high of 4,540 ml/day. The higher urine volumes were seen in patients with mild AKI with ATN (polyuric) or in the early recovery or diuretic phase of ATN. Of the 18 patients where volumes were recorded, 7 were oliguric (<500 ml/d) and 11 were polyuric. The mean time to recovery in those patients that survived was > 7 days with a range of 4 days to discharge on hemodialysis. None of these patients were on diuretics. The mean drop in the serum creatinine was 4.42 mgs/dl.

In 27 of the 28 patients, there were 14 female and 13 male patients with a mean age of 47.9 years in 20 of the 28 patients. Their ages ranged from 1 year to 81 years. Comorbidities included alcoholism 15%, cancer 15%, obesity 1 case.

Serum creatinines were measured daily to every other day during the first 10 days of admission, and frequently after that in all patients. Measurements of urinary indices was done on admission for patients with an elevated serum creatinine or on patients whose serum creatinine increased greater than 0.5 mgs/dl during hospitalization.

Urinalyses were benign with a trace protein and 0-3 rbc or wbc/npf.

Fluid resuscitation with IV NaCl was vigorous for those patients in septic shock often with vasopressors or with large urine outputs, and restricted for patients who were fluid overloaded, in CHF or severely oliguric.

A third group of 7 patients initially presented clinically with poor perfusion states who subsequently developed ATN. Serial measurements of serum and urinary electrolytes were obtained in these patients documenting the evolution from a PRA to ATN. Two of these patients had thoracic aortic aneurysms that had ruptured, and one was an abdominal aortic aneurysm (AAA), all survived post surgery. Three of the other patients had severe acute complicated cardiovascular problems with septic shock, GI bleeding, and liver failure.

Statistical analysis was done using both the one-sample Wilcoxon signed rank test and the student t test. The P value for the urine Na/K ratio, the F_{Na} and the RFI were calculated. See Tables I and II.

Results

PRA

Table I summarizes the serum and urine laboratory data from the 42 patients who had PRA. The serum sodium, chloride and potassium were typical of most renal failure patients and are not included in the table. The mean se-

Table I. Poor Perfusion. In Table I are shown the urine Na, K, and Cl all in mEq/l and the urine creatinine in mgs/dl. Four ratios are shown, the urine Na/K ratio, the urine Cl/K ratio, the urine/plasma ratio of creatinine and the serum BUN/creatinine ratio. Also shown are the fractional excretion of Na (FENa), and the renal failure index (RFI) (sodium in urine ÷ urine Cr/plasma Cr). All 42 patients had a poor perfusion state.

Case #	Serum BUN mgs/dl	Serum Cr mgs/dl	Urine Na/K	Urine Cl/K	FNa	RFI	U/P Creat	BUN Creat	Loop Diuretic
1	132	3.6	0.26	<0.32	0.18	0.26	46	37	
2	106	2.9	<0.12	<0.18	0.18	0.23	36.6	36.5	Yes
3	30	1.6	0.89	0.93	0.69	1.1	65.2	187.5	Yes
4	45	2.9	<0.19	<0.28	0.08	1.1	90.3	15.5	
fv5	50	2.2	<0.2	<0.24	0.32	0.45	24.6	22.8	Yes
6	53	2.1	0.28	<0.42	0.08	1.0	9.4	25.2	
7	93	6.5	0.16	<0.24	0.35	6.5	23	14.3	
8	93	1.6	0.16	<0.25	0.14	0.18	47.5	58.1	
9	42	3.0	0.74	1.0	1.09	2.2	19	14	
10	48	2.9	0.59	0.57	1.83	2.2	14.3	16.6	
11	180	6.1	0.45		1.39	17	10.9	29.5	
12	38	1.9	0.1	<0.14	0.5	0.59	186.9	20	Yes
13	159	3.4	0.45	0.38	1.39	1.9	10.9	46.8	Yes
14	101	3.6	<0.14	<0.21	0.32	0.43	23.1	28.1	Yes
15	40	2.8	0.32	<0.44	0.5	0.27	16	38	
16	63	2.2	<0.13	<0.19	0.2	0.26	35.4	28.6	Yes
17	76	6.7	0.53	0.74	1.3	1.7	13	11.3	
18	107	4.5	0.18	<0.25	0.35	0.47	23.6	23.8	Yes
19	63	6.5	0.3		0.66	0.88	20.5	9.69	
20	77	2.9	0.49	0.56	1.88	2.5	11.7	26.6	
21	25	1.8	0.21	<0.29	0.18	0.16	68.9	13.9	
22		5.2	0.25	0.63	1.01	1.3	13.8		
23	38	1.0	0.17	0.25	0.17	0.1	40	38.0	Yes
24	109	2.8	0.18	0.27	0.35	0.46	21.8	38.9	
25	66	1.6	0.27	0.41	0.24	0.34	29.4	41.25	Yes
26	49	3.0	0.61	.91	1.05*	2.13*	7.7*	16.33*	
27	76	4.6	0.19	0.6	1.02*	1.23*	8.11*	16.5*	
28	146	4.5	0.34	0.71	0.26	0.38	26*	32.4	
29	47	4.1	0.3		0.4	0.47	21.49*	11.46*	
30	109	2.7	0.2	0.3	0.48	0.67	14.96*	40.37	
31	34	2.6	0.15	0.21	0.18	0.26	50	13*	
32	45	3.2	0.46	0.75	0.58	0.8	43.6	14*	
33	34	2.6	0.17	0.21	0.19	0.26	50	13.1*	
34	65	2.7	<0.53	0.95	0.1	0.14	72.2	24.1	Yes
35	53	2.2	<0.27	0.42	0.66	0.09	109.1	24.1	
36	125	14.8	0.85	1.14*	0.89	1.18*	17.86*	8.45*	
37	79	2.5	0.27	0.4	0.19	0.27	37.36*	31.6	
38	66	5.2	0.35	0.43	0.13	0.16	79.81	12.7*	
39	30	2.4	0.19	0.32	0.18	0.25	39.54	12.5*	
40	126	4.5	0.3	0.33	0.24	0.32	31.11*	28	
41	51	4.9	0.42		0.54	0.73	28.78*	10.4*	
42	147	2.4	0.3	0.23	0.43	0.6	36.9*	61.25	
Mean	74.8	3.8	0.320	0.45	0.543	1.300	37.5	19.7	
SD			0.199	0.263	.543	2.728	32.882		
P value			<.0001	<.0001	<.0001	<.058			

rum K was at the upper range of normal and varied from a low of 3.4 to a high of 6.4 mEq/l. The BUN varied from a low of 25 to a high of 180 mg/dl. The BUN determination was not done in 1 patient. The serum creatinine varied from a low of 1.6 mg/dl to a high of 14.8 mg/dl.

The urine chemistries were of considerable interest. The urine sodium varied from a low of 4 to a high of 63 mEq/l. Eleven of the 42 patients had a urine sodium of > 20 mEq/l. The urine chloride paralleled the urinary sodium, however the urinary potassium was always greater than either the urinary sodium or chloride concentration and varied from a low of 16.4 mEq/l to a high of 105 mEq/l (see Table I).

The major reason for this study was to compare the urinary sodium/potassium ratio (U_{Na}/U_K) ratios with all other indices commonly used in the evaluation of AKI. In all 42 cases of PRA the U_{Na}/U_K was less than one, with ratios varying from 0.1 to 0.89 and a P value < .0001. The urinary chloride/potassium ratio (U_{Cl}/U_K) was also very low with a mean of .45. However it was not as consistent as the U_{Na}/U_K ratio and values varied from 0.18 to 1.14. The urine to plasma ratio of creatinine (U/P creat) ranged from a low of 7.7 to a high of 186.8. In 13 of the patients the U/P creatinine was less than 20 and in 28 of the patients the ratio was < 40. The mean BUN/Cr ratio was 25, and 17

Table II. ATN (Acute Parenchymal Renal Disease). Table II shows the same indices described in Table I but for the 28 patients with acute tubular necrosis.

Case #	Serum BUN mgs/dl	Serum Cr mgs/dl	Urine Na/K	Urine Cl/K	FNa	RFI	U/P Creat	BUN Creat
1	60	6.1	2.0	2.14	3.2	3.14	17.54	10.2
2	57	5.8	1.41	1.65	6.8	9.03	7.2	10
3	48	4.3	1.69			1.06	13.02	11.16
4	57	1.5	3.73	4.57		38.6	2.93	38
5	53	4.7	7.08	7.31	15	20.4	4.47	12.83
6	125	7.9	3.12	<0.9	4.9	6.6	7.59	15.82
7	30	2.0	6.64	3.96	11.73	17.5	9.5	15
8	63	2.6	2.07	2.87	16.7	23.8	3.85	24.23
9	85	5.5	5.4	4.2		18.6	3.4	15.44
10	84	5.5	3.67	4.62		32.1	2.88	15.3
11		1.8	1.12	1.61		1.7	32.2	
12	86	8.2	2.1	1.3		19	3.9	10.5
13		4.8	5.14	5.48		20.8	5.21	
14	46	3.4	1.68	1.19		3.1	20	13.5
15	65	2.3	1.28	1.53		6.9	8.7	28.3
16	125	8.7	4.73	<.99		12.7	5.63	14.1
17		4.2	2.75	4.08		6.3	10.48	
18	42	32	2.83	2.44		11.2	9.06	13.1
19	82	7.8	4.31	3.94	12.1	16.4	4.23	10.5
20	35	5.4	2.27	1.58	30.8	4.26		6.48
21	125	16.8	1.14	1.14	3.7	4.66		7.44
22	23	2.1	3.8	2.04	1.09*	1.51		10.95
23	120	3.8	2.77		3.6	5.13		31.58*
24	75	2.6	1.28	0.78*	2.54	3.54		28.85*
25	23	2.7	5.45	6.23	22.85	31.6		8.5
26	25	2.2	9.39	9.51	3.85	5.2		11.36
27	54	3.0	3.44		6.9	9.62		18*
28	74	8.7	5.2	2.13	5.6	6.92		8.51
Mean	61.6	5.3	3.86	3.34	8.99	8.05		14.63
S.D.	40.1	4.8	2.57	3.14	10.43	9.11	7.19	9.47
P value			<.0001	<.0001	<.0001	<.0001		

of the patients had a ratio < 20. Nine of the patients had a FE_{Na} > 1.0 with values ranging from 0.08 to 1.83 with a P value also < .0001. Urine volumes varied from 22 ml/day to 2100 ml/day. Most of those with larger volumes were on a loop diuretic. The loop diuretics did not appear to have any effect on the U_{Na}/U_K. The renal failure index (RFI) in these 42 patients had a low of 0.1 to a high of 17.14 and 13 of the 42 had a RFI > 1, P value 0.058 (See Table I).

ATN

In Table II are shown the same parameters, that are depicted in Table I, for the 28 patients with ATN, all of which had clinical diagnoses and courses consistent with ATN. The serum sodium and chloride were similar to the normal patients. Serum K varied from a low of 2.8 to a high of 5.8 mEq/l. The BUN varied from 23 to 125 mg/dl. Three patients did not have a BUN drawn on days when urine electrolytes were done. The serum creatinine varied from 1.5 to 16.8 mg/dl. Many of these patients were 65 to 80 years of age with presumably poor muscle mass which may have accounted for the less than expected rise in creatinine, but was still higher than the mean 3.62 mg/dl in the PRA patients.

The urine sodium concentration varied from a low of 39 to a high of 166 mEq/l. All but one of the patients had a urinary sodium concentration > 40 mEq/l. The mean urine chloride concentration was 64.2 mEq/l and generally paralleled the urine sodium concentration. Three patients did not have a urine chloride measurement and 6 patients had urine chlorides much less than the urine sodium. The mean urinary creatinine was 41.7 mg/dl and varied from a low of 4.4 mg/dl to a high of 145.6 mg/dl.

As expected the urinary indices were markedly different from the patients with PRA. The mean U_{Na}/U_K was 3.48 as compared with a mean of 0.33 for PRA. The ratios ranged from a low of 1.12 to a high of 9.39 and no patients had a ratio < 1.0, P value < .0001. Similarly the U_{Cl}/U_K ratios had a mean of 3.05 but in 3 of these patients the ratios were slightly less than 1.0. The U/P creatinine ratio ranged from a low of 1.33 to a high of 17.54. The mean BUN/creatinine ratio was 15.55 with 8 patients having a BUN/Cr of > 15.0. The FE_{Na} in the 16 patients with data available for calculation varied from 1.09 to 30.8. The RFI varied from a low of 1.06 to a high of 38.6. No values were < 1 for either the FE_{Na} or the RFI and both had P values < .0001. The urine output ranged from 100 ml/d to a high of 2420 ml/day. Once again, loop diuretics appeared to have little effect on the U_{Na}/U_K.

PRA Developing into ATN

Seven other patients had clinical courses consistent with PRA that evolved into ATN. Serial measurements of se-

rum and urinary electrolytes and indices depict their progression (Figure 1). Collections on day 1 and 2 were taken when the patient had PRA while collection 3 was done on day 3 when the patients had developed ATN.

The U_{Na}/U_K was .36 on day 1 (PRA) and increased to 2.9 on day 3 (ATN). The FE_{Na} had a mean of 0.86 on day 1 during PRA and increased to 4.18 when ATN developed. The renal failure index in the patients with poor perfusion had a mean value of 1.67 on day 1 during PRA. When these same patients developed ATN on day 3 their RFI had a mean of 13.7.

Since we did not measure the urine urea, we were unable to calculate and therefore unable to compare the fractional excretion of urea with the U_{Na}/U_K and other renal indices. However, the fractional excretion of urea requires the simultaneous measurement of both serum and urine urea and creatine concentrations.

Discussion

In hospital AKI is a common complication of many different disease states including sepsis, shock, toxic exogenous and endogenous substances, dehydration, CHF, acute and chronic liver failure, as well as many other causes. Recent studies of long-term outcomes of AKI secondary to ATN [7] have shown increasing chronic renal failure (CRF) as a long-term complication, particularly in the elderly, and an increased mortality during the acute hospitalization [8,9,10,11]. In the acute hospital setting it is also important to differentiate between ATN and PRA since the treatment with fluids and various medications will be altered by the underlying cause of the AKI. For these reasons it is important to differentiate between PRA and ATN. Obviously, a renal biopsy would differentiate between these conditions and was one of the modalities utilized in the 50's and 60's to make this diagnosis but is now reserved for patients in whom the cause of AKI is obscure [12].

In 1970, Bricker [1] proposed, based on the difference in the pathophysiology of PRA and ATN, that the urine sodium should be less than 20 mEq/l and often less than 10 mEq/l in PRA and greater than 40 mEq/l in patients with ATN[1]. Other authors proposed that a urine sodium of < 20 mEq/l for PRA and > 30 mEq/l for ATN should be used [2]. However, it was noted that there was considerable overlap between PRA and ATN, so other investigators looked for tests that would more accurately discriminate between these two conditions.

In 1967 Handa and Morrin [3] proposed measuring the RFI which was largely dependent on the fractional excretion (FE_{Na}) of sodium proposed by Espinel [4] and generally paralleled the FE_{Na}. These indices proved to be much more accurate than the urinary sodium concentration, BUN/creatinine ratio or measurements of the urine osmolality. Miller and Anderson using the RFI and FE_{Na} found very little overlap between PRA and ATN [13]. However they did find some overlap in patients with non-oliguric acute renal injury. Anderson et al. found intermediate values between PRA and oliguric ATN in non-oliguric AKI patients [14].

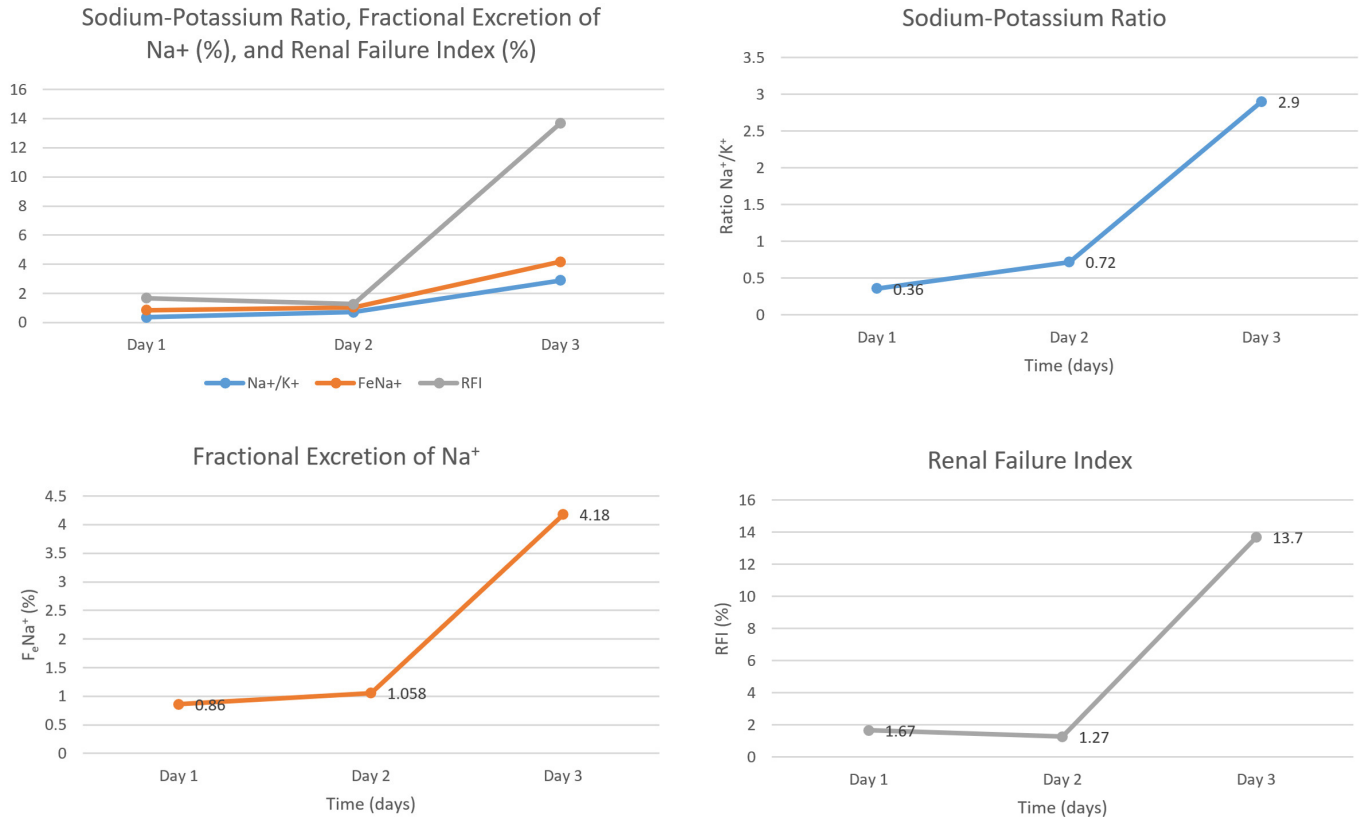

Fig.1. The results of the same 3 indices (U_{Na}/U_K, F_{Na}, RFI) used in the 7 patients who presented with severe PRA which developed into ATN. Days 1 and 2 were prior to the development of ATN while day 3 was during AT

Carvounis et. al. [5] proposed measuring the fractional excretion of urea (FEUN) in an attempt to differentiate a prerenal state from ATN. If the FEUN was < 35% the patients had PRA. In the 102 patients they studied 50 had PRA and some of these patients were on diuretics, 25 had ATN. The FEUN was more sensitive than the FE_{Na} in differentiating prerenal azotemia from ATN especially if the PRA patients had received diuretics. In their study they also looked briefly at the U_{Na}/U_K ratio. It was less reliable, but only summary data was presented and was contrary to our findings.

In a well-designed and carefully controlled study on female Marino ewes, studied before and after the onset of sepsis, Langenburg et. al. [15] concluded that "urine chemistries and indices are unreliable in sepsis and probably in other pathophysiological states." However, our data on the U_{Na}/U_K index was a reliable indicator in differentiating PRA from ATN in all causes of PRA and ATN including sepsis.

In the most recent edition of Brenner and Rector [16] a table listing all of the measurements used to differentiate PRA from ATN is presented. Nine different tests or calculations were used to try to differentiate between PRA and ATN. Other researchers [18] have noted that changes in the serum creatinine and on urine output do not identify early changes of intrinsic kidney injury which may be the most opportune time for pharmacological intervention. Coca et al., Moriates et al., Pickering et al., and Cruz et al. [19,20,21,22] have measured multiple urinary biomarkers to determine if and when tubular injury occurs. The four biomarkers studied were: kidney injury molecule 1, interleukin 18, cystatin C and neutrophil gelatinase-associated lipocalin (NGAL). Their studies were focused on trying to predict AKI, primarily ATN, by a rise in the biomarker before a rise in serum creatinine. The rise in the biomarker was attributed to severe ischemia, necrosis or inflammation of the renal tubular cells causing cell damage. The studies were prospective and did not look at patients presenting with renal failure or patients with pure poor perfusion such as dehydration, heparenal syndrome, etc. The biomarkers were also elevated in renal inflammatory states and chronic kidney disease. These biomarkers are expensive and have not been validated on a large population of AKI patients. While many of these biomarkers are increased by tubular injury they are also increased by other disease states, many of which accompany or cause ATN (23). Further studies need to be done on these biomarkers on a patient population with both ATN and PRA to determine if they can accurately differentiate between these two disease states of AKI.

A simple inexpensive test that would accurately differentiate between PRA and ATN, cause less patient discomfort, aid in the treatment, and at the same time be cost effective, should be of major interest.

A careful understanding of the pathophysiology of PRA and ATN should be of help in devising such a test. In PRA there is a decrease in the effective arterial volume (EAV) but most nephrons are still functioning, albeit at a low level, with a decrease in GFR but intact tubular function, but very capable of transporting sodium and potassium in the distal nephron. The decrease in the EAV is associated with a decrease in the pressure in the juxta-glomerular (JG) apparatus with an increase in renin and the subsequent increase in both antiogensin and aldosterone. Not only is sodium actively reabsorbed in the proximal convoluted tubule, thick ascending limb of Henle's loop and the distal convoluted tubule, but much of the sodium escaping reabsorption at these sites is taken up in the connecting tubule and cortical collecting duct in exchange for potassium under the influence of the increased levels of aldosterone strongly suggesting intact function of the tubules. As a result there is significantly less sodium delivered into the urine but increased potassium excretion. Therefore, with PRA, the decreasing urine sodium and increasing urine potassium diverge in the urine. In acute tubular necrosis probably in excess of 95% of the nephrons are badly injured and most of the nephrons contribute little to the function of the kidney. These nephrons with injured tubules are incapable of reabsorbing Na and secreting potassium causing a loss of sodium in the urine but minimal potassium secretion. A second reason for impaired sodium reabsorption and potassium secretion could be due to the translocation of Na^-/K^+-ATPase from the basolateral membrane to the cytoplasm, in ATN, which could significantly impair sodium reabsorption in exchange for potassium secretion [17]. So once again sodium and potassium excretion go in opposite directions with a high urine sodium and limited K excretion. Therefore an analysis of the urine Na/K ratio should accurately differentiate these two states.

In an attempt develop a test that fulfilled the prior criteria we looked at more than 200 patients with AKI at the Loma Linda Medical Center and the Redlands Community Hospital over a period of one to two years. These two hospitals were chosen since the investigators were working at these hospitals at the time of study. Twenty-eight of these fulfilled the criteria for ATN (2 proven by renal biopsy) and 42 fulfilled the criteria for PRA. Another 7 patients had PRA that evolved into ATN. We measured the U_{Na}/U_K and U_{Cl}/U_K ratios and compared them to all the previous indices that have been reported.

From Tables I and II it readily becomes apparent that the BUN/creatinine ratios, the urine to plasma creatinine ratios and the U_{Na} are notoriously inaccurate in differentiating between PRA and ATN and therefore should be discarded in the workup of AKI. The FE_{Na} and RFI are much more accurate in diagnosing AKI due to ATN but still have significant overlap in patients with PRA. In 13 of the 42 patients with PRA the RFI was greater than 1 (30%), while in 9 patients the FE_{Na} was greater than 1 (21%). The U_{Na}/U_K ratios were less than 1 in all 42 patients (100%).

The data we have presented on the U_{Na}/U_K show 100% sensitivity and specificity in differentiating PRA from

ATN. In only one patient with ATN where the U_{Na}/U_K ratio was less than 1 (case 1) (Table III) was a patient where the PRA was developing into ATN, and the U_{Na}/U_K ratio was increasing rapidly but was still <1. A larger prospective study should be done on the urinary Na/K ratio, and it may show a lower sensitivity and specificity in the urinary Na/K ratio.

Conclusion

We believe the U_{Na}/U_K ratio after further prospective studies may become the preferred test to differentiate PRA from ATN in AKI for the following reasons: First, it is a much more accurate and reliable test than those presently in use to differentiate between PRA and ATN. It appears to have 100% sensitivity and specificity and therefore may eventually replace all other tests for AKI if it is found to be a more accurate diagnostic test in AKI. Second, it requires only a spot urine specimen for Na and K, and no timed urine collections are required. Third, it does not require drawing any blood samples and does not rely on the appraisal of muscle mass and creatinine production. Fourth, because of its ease of testing, it could be done in poor perfusion states repeatedly to determine if and when the patient may be converting from PRA to ATN so that medication and fluid administration can be adjusted, avoiding fluid overload and CHF and medication overdose. And fifth, it could save considerable costs in the care of patients with AKI.

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Conflict of Interest

None to declare.

Authors' contribution

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Table III. Poor Perfusion ® ATN. The 7 patients in Table III all began their clinical course with a poor perfusion state which subsequently developed into acute tubular necrosis. The same indices depicted are described in Table I. Studies a & b were collected during the poor perfusion phase of their illness, while studies c & d were collected during the acute tubular necrosis phase.

Case #	Serum BUN mgs/dl	Serum Cr mgs/dl	Urine Na/K	Urine Cl/K	FNa	RFI	U/P Creat	BUN Creat
1a	10	0.6	0.12	0.71	.08	.1	191.7	16.7
b	24	1.7	0.2		0.3	.4	62.9	14.1
c	42	3.0	0.74	1.0	1.6	2.21	19	14
2a	31	2.4	0.17	.49	0.2	3.5	45.4	12.9
b	5.3	4.5	1.63	2.95	2.4	29.9	3.8	11.8
d	7.5`	6.2	4.19	3.83	4.1	41.2	2.7	12.1
3a	8.7	3.9	0.62	<0.32	0.6	1.23	22.3	23.6
c	132	5.6	2.04	1.90		5.83	23.6	9.11
4a	59	2.9	0.39	<0.20	0.5	.75	38.6	20.3
c	65	22	2.28	1.81	3.2	7.26	13.5	18.2
d	104	5.7	2.28	1.81	3.2	7.26	13.5	18.2
5a	25	1.7	<0.19	<0.29	0.6	.12	83.5	14.7
b	40	2.8	<0.2	1.1	.27	.31	32.5	14.3
c	89	5.9	5.12	3.62	10.8	17.9	15.08	4.6
6a	49	3.3	0.91	0.81	3.1	4.36	13.3	14.8
c	67	3.8	3.04	3.93	15.8	21.1	17.6	3.7
7a	109	3.4	0.12	0.67	1.16	1.63	7.4	32.1
b	126	4.4	<0.12	0.28	1.03	1.47	6.8	28.6
c	93	4.2	35.7	35	165.9	201.2	0.69	22.1
Mean a & b	56	2.71	0.30	0.54	0.78	1.07	50.44	19.21
S.D.	±37	±1.1	±0.25	±0.28	0.84	1.22	52.55	6.4
Mean c & d	70	4.56	6.38	6.07	6.99	39.82	14.95	13.91
S.D.	±26	±1.32	±10.44	±10.29	6.02	60.39	11.24	7.84

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