Urinary Electrolytes, Solute, and Osmolality

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Urinary tests are becoming increasingly popular because of ease of collection and some advantages to serum testing. Although plasma osmolality (POsm) and solute concentrations must exist in narrow ranges for proper cellular function, the chemical composition of urine can vary widely. The kidneys change the composition of urine to facilitate normal homeostasis and react to systemic challenges. Analysis of urine chemistry is vital in determining if the kidneys are functioning adequately for homeostasis and can appropriately respond to insult and injury.

The volume and elements that comprise urine depend on the actions of the kidneys in filtration of blood in addition to reabsorption and secretion of water and solutes. As plasma passes through the glomerulus, macromolecules (eg, proteins) and cellular elements, such as cells and proteins, are selectively retained based on charge and size. The remaining filtrate continues through the tubule and is subjected to various passive and active mechanisms that result in retention or excretion of solutes and water. The amount of solutes excreted is determined by dietary intake, renal threshold for reabsorption, hormonal influence, or a combination of these factors. Some solutes are freely filtered but neither reabsorbed nor secreted (eg, creatinine [Cr]), whereas other substances may be released by the kidney in response to damage (eg, brush border enzymes) [1,2].

Defining normal urine composition is problematic, because there can be wide intra- and interindividual variability in the amount of solutes and water in the urine of healthy animals [2–4]. Urine chemical concentrations from different breeds may even be different under normal circumstances [4,5]. This can make interpretation of urine chemistries difficult. As is the case with some other indicators in critical patients (eg, central venous pressure, lactate), trends and changes over time may be more important than individual concentrations. The use of drugs, including diuretics, parenteral nutrition, and fluid therapy, also can interfere with urine chemical analysis. This article outlines some of the clinically useful urine chemistry tests and addresses their limitations.

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URINE SOLUTE MEASUREMENTS

The interpretation of urine chemistries can vary widely based on the urine collection method. A solute’s concentration can be determined using a random sample or by 24-hour collection. Random samples can be less accurate, especially when the urine is dilute [1,6,7]. The 24-hour urine collections are laborious and usually require hospitalization, but if a urinary catheter is present, shorter timed collections may be possible [8]. Given that Cr clearance reflects glomerular filtration rate (GFR), calculation of the relative ratio of the solute to creatinine may be useful (eg, urine protein/urine creatine [UPr/Cr] ratio). By comparing the urine concentrations of the solute and Cr with the plasma concentrations, the fractional excretion (FE) can be calculated. When the FE ratio is less than 1.0, the solute has net reabsorption, and if the ratio is greater than 1.0, the solute has net secretion [1,7]. Unless used chronically, diuretics should be withheld for 6 to 8 hours before the measurement of any urine chemistry.

The equations to calculate the FE of a solute and the renal failure index (RFI) are as follows:

\[
\text{FE(solute)} = \frac{U(sol) \times PCr \times 100}{P(sol) \times UCr}
\]

\[
\text{RFI} = \frac{UNa \times PCr}{UCr}
\]

where \(U(sol)\) is urine solute concentration, \(P(sol)\) is plasma solute concentration, \(PCr\) is plasma creatinine, \(UCr\) is urine creatinine, and \(UNa\) is urine sodium.

URINE SODIUM AND CHLORIDE

Commonly measured urine electrolytes include sodium (Na) and chloride (Cl). Evaluation of the urine concentration of these two electrolytes aids in differentiation of hypovolemia and renal tubular dysfunction in patients that have azotemia. Sodium balance is regulated by two related and interdependent systems: osmoregulation and volume regulation [1]. Serum concentration in the extracellular fluid is controlled in a narrow range by the hypothalamus. Osmoreceptors signal changes in water intake and excretion based on changes in POsm. Antidiuretic hormone (ADH) is released if water needs to be conserved and acts on the renal collecting ducts to maximize water reabsorption. ADH targets the V2 receptors on the collecting duct cells, signaling the downstream insertion of water channels, called aquaporins, into the luminal membrane. Without ADH, the aquaporins are removed and urine is maximally dilute [1,2].

By regulating the absolute amounts of Na and water, the body determines the effective circulating volume. Volume changes are sensed by stretch receptors throughout the vascular tree (eg, aortic arch, afferent arteriole, atria, carotid sinus). Changes in volume lead to secretion of various hormones to affect sodium absorption or secretion (Table 1). Cl usually follows Na, and as more solute is retained or discarded, water moves secondarily. With a substantial decrease in effective circulatory volume, volume receptors signal...
the release of ADH as well, allowing further retention of water. With severe hypovolemia, the preservation of cardiac output “trumps” the moderate hypo-osmolality that may result from maximal stimulation of ADH and water retention [1,6,7].

Given maximal stimulation of the renin-angiotensin-aldosterone system (RAAS) with hypovolemia, UNa and urine chloride (UCl) concentrations should be low (<20 mEq/L) (Table 2). UNa and UCl are high (>40 mEq/L) when the kidneys are unable to respond to normal stimuli, as in acute tubular dysfunction. Acute tubular necrosis (ATN) can occur secondary to (1) renal ischemia as may occur with hypotension, hypoxia, and sepsis; (2) prolonged prerenal azotemia; or (3) endogenous or exogenous toxins, including aminoglycoside antibiotics, nonsteroidal anti-inflammatory drugs (NSAIDs), contrast media, cisplatin, and myoglobin. A high UNa can be seen in several conditions other than ATN, including postrenal causes of azotemia, hypothyroidism, hypoadrenocorticism, and diuretic use. Any defect in Na reabsorption can lead to a falsely high UNa despite hypovolemia [1,6,9].

Table 1
Hormonal and physiologic signals affecting renal sodium excretion

<table>
<thead>
<tr>
<th>Agent</th>
<th>Effect</th>
</tr>
</thead>
<tbody>
<tr>
<td>Renin</td>
<td>Production of angiotensin I</td>
</tr>
<tr>
<td>Angiotensin II</td>
<td>↑ Aldosterone release</td>
</tr>
<tr>
<td></td>
<td>↑ Tubular Na reabsorption directly</td>
</tr>
<tr>
<td>Aldosterone</td>
<td>Distal nephron: ↑ Na/Cl reabsorption, potassium loss</td>
</tr>
<tr>
<td>Atrial natriuretic peptide</td>
<td>↓ Aldosterone and renin release</td>
</tr>
<tr>
<td></td>
<td>Collecting duct: inhibit Na reabsorption</td>
</tr>
<tr>
<td>Dopamine</td>
<td>↓ Aldosterone release</td>
</tr>
<tr>
<td>Prostaglandins</td>
<td>↑ Increase renin release</td>
</tr>
<tr>
<td></td>
<td>↑ Renal Na excretion</td>
</tr>
<tr>
<td>Sympathetic nervous system</td>
<td>↑ Intrarenal Na retention (x1)</td>
</tr>
<tr>
<td>Pressure natriuresis</td>
<td>↑ Intrarenal Na loss</td>
</tr>
<tr>
<td>Hyperkalemia</td>
<td>↑ Aldosterone</td>
</tr>
</tbody>
</table>

Table 2
Summary of expected urine indices (measured and calculated) in prerenal azotemia and acute tubular necrosis

<table>
<thead>
<tr>
<th>Index</th>
<th>Prerenal</th>
<th>ATN</th>
</tr>
</thead>
<tbody>
<tr>
<td>UNa</td>
<td>&lt;20 mEq/L</td>
<td>&gt;40 mEq/L</td>
</tr>
<tr>
<td>UCl</td>
<td>&lt;20 mEq/L</td>
<td>&gt;40 mEq/L</td>
</tr>
<tr>
<td>UCr/PCr ratio</td>
<td>&gt;40</td>
<td>&lt;20</td>
</tr>
<tr>
<td>FENa</td>
<td>&lt;1%</td>
<td>&gt;2%–3%</td>
</tr>
<tr>
<td>RFI</td>
<td>&lt;1</td>
<td>&gt;2</td>
</tr>
<tr>
<td>UOsm/POsm ratio</td>
<td>&gt;1.5</td>
<td>1.0–1.5</td>
</tr>
</tbody>
</table>

Abbreviations: ATN, acute tubular necrosis; FENa, fractional excretion of sodium; UOsm/POsm, urine osmolality–to–plasma osmolality ratio.
A gray zone exists between a UNa of 20 and 40 mEq/L, wherein overlap can occur. A low UNa can be seen in normovolemic animals when selective renal or glomerular ischemia has occurred secondary to severe decreases in renal blood flow or acute glomerulonephritis (GN). A single UNa can be measured, but 24-hour collections and comparisons with Cr clearance are most useful. Interpreting a single UNa is difficult, and comparison of a few renal indices is advised in the medical literature [1,6,8,9]. The presence of any underlying chronic renal disease negates the utility of UNa and UCl.

Alterations in urine water concentration also make interpretation of UNa difficult. A classic example is central diabetes insipidus (CDI). The lack of ADH allows maximally dilute urine and a low UNa. Most animals with CDI have achieved volume balance with severe polydipsia and are not hypovolemic unless a crisis occurs. Calculating the fractional excretion of sodium (FENa) removes water balance from the equation by adjusting for GFR. A FENa greater than 2% is consistent with a UNa greater than 30 mEq/L and indicates that the observed azotemia is not likely prerenal. Calculation of the FENa is most sensitive when polyuria is not present but may provide the most information when used in combination with other renal indices.

UCl and fractional excretion of chloride (FECl) usually add little information to that provided by UNa and FENa [1,6,7,10]. Both should be calculated and compared when trying to differentiate prerenal azotemia from ATN (see Table 2). If there is a difference of more than 15 mEq/L between UNa and UCl in a hypovolemic animal, it is likely attributable to the excretion of Na with another anion (eg, bicarbonate) or Cl with another cation (eg, ammonia). It currently is recommended in the medical literature that UCl be measured in patients that are hypovolemic but have a somewhat increased UNa. This most commonly occurs in metabolic alkalosis because of excretion of Na with bicarbonate (UCl <20 mEq/L) [6,7]. A UCl less than 20 mEq/L also can occur secondary to exogenous or endogenous corticosteroids [1].

Table 2 summarizes the expected values for urine Na and Cl indices and includes other calculations cited in the medical literature to differentiate ATN and prerenal azotemia [1,7,9]. The use of these indices in the medical field has been standardized, and there are many on-line calculators for FENa and RFI (including Refs. [11,12]). The use of these urinary indices in veterinary medicine has not been verified but may be available in some cases of acute toxic or ischemic injury to the kidneys. Urinary indices, such as UNa and FENA, should be used in conjunction with standardized testing, including PCr, blood urea nitrogen (BUN), and urine output [7,8].

There are three clinical scenarios in veterinary medicine in which measurement of UNa and UCl may be most useful: (1) NSAID toxicity, (2) monitoring aminoglycoside use, and (3) after severe hypotension. Episodes of severe hypotension may occur with shock, anesthesia, or cardiopulmonary arrest. Monitoring UNa and UCl after successful cardiopulmonary resuscitation may be helpful to monitor for signs of substantial renal damage. This has not yet
been studied in veterinary medicine but could be clinically useful when multiple renal indices are measured and compared.

Common treatments for NSAID toxicity include diuresis, activated charcoal, and prostaglandin (PG) E₁ analogues. Serial measurements of BUN and PCr are monitored to determine if there is clinically relevant renal damage, because urine osmolality (UOsm) is not likely to be helpful in the face of diuresis. At presentation, many animals may have moderately concentrated urine, which can make it difficult to determine if they had limited renal function before ingesting toxic doses of NSAIDs. Measurement of UNa and UCl on entry and serially may help to indicate substantial renal toxicity before increases in BUN and PCr, which may not occur for 36 to 48 hours after ingestion. In the author’s experience, urine indices have been helpful in several cases and are widely available and inexpensive.

Monitoring for aminoglycoside toxicity is also difficult, given that considerable damage may occur before the BUN and PCr are increased. Other urine markers of early renal damage include brush border enzymes, glucose, and casts. In one pediatric study, urinary losses of Na, magnesium, and calcium were significantly increased after a single dose of aminoglycosides, but renal damage was not noted in that clinical study [13]. It is not known whether urinary measurements of Na and other electrolytes can identify animals more likely to incur renal damage or may just highlight animals that are prone to urinary electrolyte wasting. Aminoglycosides are widely used in veterinary neonates (eg, septic foals, dogs with parvoviral enteritis), however, further investigation into the clinical usefulness of urine chemistries with aminoglycoside use is needed in veterinary medicine.

Sepsis is a common cause of disease in animals, and considerable renal damage can occur secondary to inflammation, thromboembolism, and decreased renal perfusion. The use of urinary indices to document ATN in sepsis is still open to debate. A recent review of the available medical literature linking urinary indices and experimental models of acute renal failure and sepsis found significant variability in the ability of urinary indices to diagnose acute renal injury [14]. Acute renal failure induced by gram-negative sepsis in ewes did not cause urinary indices to change any established pattern [15].

PCr is an established marker for GFR, as discussed previously, and is an extremely reliable marker of renal function. Small changes in PCr can indicate severe loss of function even when the PCr is in the “normal” range [8]. A comparison of UCr and PCr is another way to estimate tubular water reabsorption. Patients with prerenal causes of azotemia generally reabsorb most water and have a UCr/PCr ratio greater than 40 (see Table 2) [1].

**OSMOLALITY**

Osmolality is defined as the number of solute particles per kilogram of solvent. The major determinants of extracellular and intracellular fluid osmolalities are Na and potassium (K) respectively, whereas UOsm reflects a more heterogeneous mixture of solutes. Urine solutes include urea, Na, K, ammonium...
(NH₄), Cl, and other anions [1,2,7]. UOsm can be estimated (UOsm = Urea + 2[Na⁺+K⁺+NH₄⁺]) or measured by freezing point depression osmometry. Normal UOsm can range widely between 800 and 2500 mOsm/kg in the dog and between 600 and 3000 mOsm/kg in the cat [2,16]. In contrast, normal POsm ranges between 290 and 330 mOsm/kg for dogs and cats [2].

Urine specific gravity (Usg) is a more useful test clinically and is usually measured using a refractometer. Specific gravity is considered a valid estimation of osmolality if the urine does not have high concentrations of glucose, proteins, or molecules (eg, radiocontrast agents) [1,2,17]. UOsm can be calculated from Usg with the following equation: UOsm = (Usg – 1.000) × 40,000 (Table 3) [17].

Water can be actively reabsorbed in the presence of ADH and passively lost with large solute loads. Maximal water reabsorption can only be attained with adequate hypertonicity of the renal medulla (countercurrent multiplier effect) and appropriate responsiveness of the collecting duct cells to ADH. In the normal animal, water reabsorption or loss is determined by water intake, POsm, and effective circulating volume. The retention of some solutes, such as Na and Cl, aid in water retention [1,2].

The clinical importance of measuring UOsm is most obvious in differentiating prerenal and renal causes of azotemia and verifying that at least 33% of the kidney mass is functioning adequately. A concentrated urine sample (UOsm >1200 mOsm/kg, Usg >1.035) is found when renal concentrating function is adequate. There are conditions under which the expected UOsm may not be found, however, despite signs of azotemia or dehydration and adequate renal function. Clinically important conditions that may cause hypotonic urine include any cause of polyuria and polydipsia (eg, diabetes mellitus, hyper- or hypoadrenocorticism), medullary washout secondary to fluid administration, sepsis, and pharmacologic agents (eg, corticosteroids, diuretics).

Another common use of UOsm in combination with UNa in the medical field is for the diagnosis of the syndrome of inappropriate antidiuretic hormone secretion (SIADH), a major cause of hyponatremia in human beings. SIADH has rarely been reported in veterinary medicine and is an “umbrella” term for a variety of causes of hyponatremia [18]. When vascular volume is essentially normal but hyponatremia persists, ADH secretion is inappropriate. A diagnosis of SIADH is one of exclusion, and possible causes in people include neoplasia, central nervous system disorders (eg, stroke, masses, trauma),

### Table 3
Comparison of urine osmolality and corresponding specific gravity

<table>
<thead>
<tr>
<th>UOsm (mOsm/kg)</th>
<th>Usg</th>
</tr>
</thead>
<tbody>
<tr>
<td>40</td>
<td>1.001</td>
</tr>
<tr>
<td>520</td>
<td>1.013</td>
</tr>
<tr>
<td>680</td>
<td>1.017</td>
</tr>
<tr>
<td>1600</td>
<td>1.040</td>
</tr>
<tr>
<td>2400</td>
<td>1.060</td>
</tr>
</tbody>
</table>
pulmonary conditions (eg, positive-pressure ventilation, infections), medications (eg, chemotherapy, tricyclic antidepressants), surgery and anesthesia, pain, and HIV infection. To diagnose SIADH, the following criteria must be met: (1) isovolemic hypotonic hyponatremia; (2) normal adrenal, renal, and thyroid function, (3) high UOsm (>100 mOsm/kg) in the presence of low P0sm; (4) inappropriate natriuresis (UNa >20 mEq/L); (5) documentation of increased ADH concentration; and (6) correction of hyponatremia by water restriction [2,18].

OTHER URINE INDICES

Urine potassium (UK) and functional excretion of potassium (FEK) are affected by aldosterone and vary with dietary K intake, because serum and intracellular K concentrations are controlled in a narrow range. The most clinically useful application of UK is in the diagnosis of uroabdomen. Calculation of the abdominal fluid/peripheral blood ratio of K and Cr is highly predictive of the presence of urine in the abdomen. Schmeidt and colleagues [19] report a K ratio of greater than 1.4 (abdominal to peripheral) to be 100% sensitive and specific for dogs with uroabdomen. The measurement of plasma and urine K and Cr can be performed on an emergency basis by most in-house chemical analyzers.

Urinary calcium (UCa) and UNa may be useful to monitor the success of dietary modification in animals with urolithiasis. In the medical literature, increased UCa has been seen with many neoplastic disorders, including multiple myeloma and bone metastasis, and with corticosteroid use [6]. The clinical usefulness of UCa is limited in veterinary medicine at this time.

The loss of enzymes into the urine, or enzymuria, has been noted in a variety of renal disorders and reflects tubular cell damage [20]. Increases in urine N-acetyl-β-D-glucosaminidase (NAG) occur when more protein is presented to the renal tubular cells, and therefore increases lysosomal activity and excretion of NAG. Alkaline phosphatase and γ-glutamyl transpeptidase (GGT) are too large to be filtered through the glomerulus; therefore, their presence in urine reflects leakage from the proximal tubule brush border cells. As with other urine indices, an enzyme-to-Cr ratio may be more accurate. Establishing a baseline for enzymuria before renal injury may be a limiting factor in clinical practice.

Enzymuria has been documented as an early marker of renal disease in many species, including the dog, cat, and cow [21]. For example, renal function has been studied using urine enzymes in pyometra [22], anesthesia [23], leishmaniasis [24], and NSAID use [25]. Urine NAG is increased in some dogs with pyometra even after spaying, indicating continued renal tubular damage [22]. Urine alkaline phosphatase, GGT, and NAG have been used as early markers of aminoglycoside nephrotoxicity. In one study, a threefold increase of urine GGT over baseline preceded changes in Usg, proteinuria, and PCr concentration after administration of a toxic dose of gentamicin [26].

Novel urine indices have been used in a variety of diseases, and some may become commercially available. For example, an interesting clinical study of
canine gastric dilatation and volvulus (GDV) found that urine concentrations of 11-dehydro-thromboxane B2 (11-dTXB2) were higher in affected dogs than in healthy surgical controls before and after surgery. A postoperative increase in the urine 11-dTXB2/Cr ratio was associated with an increased incidence of postoperative complications. Thromboxanes are generated after perfusion is restored to ischemic tissues, and excretion of thromboxane metabolites, such as 11-dTXB2, in the urine has been associated with myocardial infarction and atherosclerosis [27].

**PROTEINURIA**

UPr testing is one of the more established urine chemistries. Evidence of proteinuria can indicate loss of proteins secondary to many causes, including prerenal (eg, multiple myeloma), renal (eg, GN, tubular damage), or postrenal (eg, bladder neoplasia) disorders. Single UPr measurements are not sensitive, especially typical dipstick methods. Use of the UPr/Cr ratio is sensitive to significant protein loss, with a value of greater than 1.0 prompting immediate investigation [28,29]. Active urine sediment impairs the interpretation of the ratio, because severe infection can increase the ratio to greater than 30, but small amounts of hemorrhage, such as may occur with cystocentesis, without active pyuria may not. In an in vitro study, blood contamination of 10% total volume still only increased the UPr/Cr ratio to 1.8 [30].

Substantial proteinuria is a poor prognostic indicator in animals with chronic kidney disease (CKD) [20,28,29]. More recently, detection of microproteinuria has been advocated as an “early warning system” for CKD and other systemic diseases [28,31]. Detection of pathologic microalbuminuria (urine albumin <30 mg/dL) can be performed in-house or with more quantitative methods [20,29]. The use of the microalbumin/Cr ratio may be more accurate because it relates albumin loss to GFR.

Microalbuminuria also can be seen with many conditions that change vascular permeability. Transient microalbuminuria has been seen after exercise, surgery, burns, trauma, and pancreatitis [32]. Pathologic vascular leakage, or capillary leak syndrome, occurs systemically in response to the global release of inflammatory mediators after severe injury. Increased vascular permeability may manifest as acute respiratory distress syndrome (ARDS) or edema. Given that the kidney “is ideally placed to amplify small changes in vascular permeability” [32], microalbuminuria may occur days before other indicators of inflammation, such as C-reactive protein. A surge of microalbuminuria has been documented in posttraumatic patients that have ARDS in the first 24 hours after injury and may be an early predictor of those patients at risk for developing ARDS [33]. In another small medical study, a surge in the urine microalbumin/Cr ratio at 6 hours after admission to an intensive care unit predicted mortality [34]. Although some veterinary studies have been published examining the association of microalbuminuria and systemic disease, no study has evaluated the change in microalbuminuria that may occur with an acute systemic insult, such as septic abdomen or GDV.
SUMMARY
Urinary chemical markers are a little used clinical resource in veterinary medicine, despite their wide availability and cost-effectiveness. Interpretation of urinary chemistries should be made in light of expected renal responses and using multiple indices to avoid the limitations associated with a single urine test. Urine chemistries may be most useful in cases of acute renal damage, such as toxicities, or changes in glomerular permeability, such as capillary leak syndrome. Additional research is needed to validate the usefulness of urine chemistries to predict disease, but the veterinary clinician still can use urine chemistries in conjunction with laboratory and clinical findings.

References


