



OSMOMETRY

The Rational Basis for Use of an Underappreciated Diagnostic Tool

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INTRODUCTION

Osmometry measures the total solute concentration in a liquid. After a brief discussion of how osmometry differs from other estimates of solute concentration, methods for measuring osmolality will be presented and compared. In physiologic states, serum and urine osmolality are closely regulated to maintain normal total serum solutes. Aside from checking accuracy of solute measurements, osmometry provides measurements (osmotic gap; free water clearance) which provide immediately useful information in patient management which are not readily available in any other fashion. Several clinical case studies illustrating osmometry's importance will be presented. The importance of stat osmometry availability will be emphasized.

Upon completion of this presentation, the reader will be able to:

1. Compare and contrast the accuracy and clinical importance of various methods for estimating or measuring osmolality.
2. Calculate osmotic gap and free water clearance from routine laboratory measurements.
3. Suggest appropriate criteria for utilization of these tests in patient management.

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PROPERTIES OF SOLUTIONS

When solutes are added to a solvent, the resulting solution differs from the initial solvent in several ways. The presence of one or more solutes alters the ability of the solvent molecules to interact, reducing their freedom of movement; thus, the ability to move from liquid to solid (or liquid to gas) is altered. These changes, which collectively are referred to as **colligative properties**, are dependent on the total number of particles present in the solution. For a simple chemical, such as urea, the effect is related to the total number of moles of urea in solution. For a chemical compound which can dissociate, such as sodium chloride, both the sodium and the chloride will contribute to these colligative properties. Thus, theoretically, we would have twice the effect from one mole of sodium chloride that we would see with urea. (If the dissociation is not complete, however, the effect would be less than twice as great.) The actual mass of the particles is irrelevant for this purpose; a small molecule will exert the same effect as a large molecule. The four basic alterations due to the presence of solute are shown in Table 1. A change in any one of these properties can be used as a measure of the total molar concentration of dissolved solute in any solution. Using freezing point depression as an example, if the freezing point is lowered by 0.93°C , then there is 0.5 mole of total solute in the solution.

OSMOTIC PRESSURE

Osmotic pressure is defined as the force which would be required to resist movement of solvent across a membrane which is permeable to the solvent but not to the solute molecules. When such a membrane is present, the natural tendency is for solvent to move across the membrane in an attempt to balance the concentration of solute molecules on either side. To prevent such a movement, pressure is required (**Figure 1**). Alternatively, this can be viewed as the force which drives the movement of solvent across the membrane. One mole of solute in a solution with one liter of solvent will create one **osmole**. Measurements of osmolar concentration are often expressed as osmolarity or osmolality. Osmolarity refers to a solution with a certain number of moles of solute per **liter** of solution. Since the volume of solution changes with amount of solute added as well as with temperature and pressure, this is difficult to determine. Osmolality refers to the number of moles of solute present per **kilogram** of solvent. Since the amount of solvent will remain constant at constant temperature and pressure, this is easier to evaluate, and osmolality is the more commonly used term. Technically, osmolality should be determined

Table 1 - Colligative Properties
Change per mole solute per kg solvent

| | |
|----------------------------|------------------------|
| Freezing point depression | 1.86°C |
| Boiling point elevation | 0.52°C |
| Vapor pressure depression | 0.3 mm Hg |
| Osmotic pressure elevation | 17,000 mm Hg |

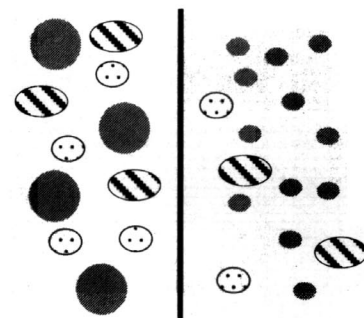


FIGURE 1 - Osmotic pressure is produced by a difference in concentration of *particles* on different sides of a membrane which allows passage of water (but not the particles); particle size is irrelevant. In this example, water moves from left to right; movement will cease when particle concentration is the same on both sides.

by osmotic pressure; however, this is not easily measured. Since osmotic pressure is directly related to total molar concentration of solutes, there is a direct and linear relationship between osmotic pressure and, for example, freezing point or vapor pressure depression. Measurements of other colligative properties are thus often expressed as osmolality, even though this is not technically correct.

RELATIONSHIP OF SPECIFIC GRAVITY TO COLLIGATIVE PROPERTIES

Specific gravity and refractive index are measures of the content of solids in a solution in comparison to water; specific gravity defines the weight of a solution relative to water, while refractive index describes the ability of a solution to bend light relative to water. If all solutes have a similar molecular weight and refractive index, then these measures will be directly proportional to osmotic pressure or other colligative properties. In normal urine, the major solutes are the waste products urea and creatinine in relatively constant proportions; there is a close relationship between specific gravity, refractive index, and osmolality. If larger molecular weight substances are present, there will be divergence between specific gravity or refractive index and osmolality. In urine, increasing glucose or protein concentration disproportionately increase specific gravity. In serum, specific gravity and refractive index are largely related to protein concentration; in many laboratories, refractive index is used to measure total protein concentration to interpret protein electrophoretic patterns. These measurements in serum are insensitive to changes in the total molar concentration of solutes and show little correlation with osmolality.

RELATIONSHIP OF IONIC STRENGTH TO COLLIGATIVE PROPERTIES

A more recent technology for estimating total solute concentration involves reagent pads on urine dipsticks which respond to changes in urine ionic strength. The predominant ionized compounds in urine are the electrolytes (sodium and potassium); waste products such as urea and creatinine and abnormal constituents such as glucose and protein are uncharged and, therefore, not measured in these tests. In normal urine, there is a close correlation between osmolality, specific gravity, and ionic strength. Because ionic strength changes do not directly relate to total solute concentration in illness, however, these tests frequently produce inaccurate estimates of osmolality. In addition, the reagent pads are sensitive to changes in urine pH (inversely related to reported specific gravity) and protein concentration

(directly related to reported specific gravity). As a result, ionic strength measurements produce misleading results in a high percentage of hospitalized patients.

METHODS FOR DIRECT MEASUREMENT OF OSMOLALITY

Because estimates of osmolality from specific gravity, refractive index, and ionic strength are frequently inaccurate, direct measurements should be used whenever precise knowledge of total solute concentration is required. Because measurement of boiling point and osmotic pressure are time consuming or technically difficult, respectively, direct osmolality measurements are usually performed by freezing point or vapor pressure depression. Both types of instruments are available for use in the clinical laboratory, and both can provide reliable measurement of osmolality in normal serum and in urine. If volatile solutes are present, as may occur with ingestion of alcohols or a few other substances, vapor pressure osmometers will not show a change in osmolality. As will be discussed below, osmotic gap is an extremely useful screen for patients suspected of taking an overdose of alcohols; such a gap will be absent if osmolality is measured by vapor pressure osmometers. If alcohol screening is needed in the clinical laboratory, then freezing point depression osmometers provide the only acceptable method for direct measurement of osmolality.

| Method | Substances Measured | Advantages | Disadvantages |
|-------------------------|--|---|---|
| | | Simple, can be read automatically, can be done near patient | |
| Specific Gravity | BUN, creatinine, electrolytes, other small M.W. solutes (e.g., glucose), protein, X-ray contrast | Simple; no expensive equipment required; can be done near patient | |
| Osmolality | BUN, creatinine, electrolytes, other small M.W. solutes (e.g., glucose) | Directly related to total molar concentration of solutes; most accurate measure of total solute; unaffected by M.W. of solute | Most expensive (initial cost of equipment); requires greater technical expertise; not commonly available near patient; vapor pressure methods insensitive to volatile solutes (alcohols, acetone) |

Table 2 - Comparison of Methods for Solute Concentration

NORMAL WATER AND SOLUTE HOMEOSTASIS

Water Compartments and Their Composition

The human body is largely composed of water; approximately 50-60% of the weight of an average person is actually water (because fat contains virtually no water, those with more fat have less water). In the body, water exists within three compartments, as illustrated in Table 3.

Table 3 - Composition of Body Fluid Compartments

| Fluid Compartment | % Total Body Water | Major Cations | Major anions | Protein Concentration |
|-------------------|--------------------|---------------|----------------------|-----------------------|
| Intracellular | 50 — 65 | K, Mg | PO ₄ | Very High |
| Intravascular | 10 — 12 | Na, K, Ca | Cl, HCO ₃ | High |
| Interstitial | 25 — 40 | Na, K, Ca | Cl, HCO ₃ | Very Low |

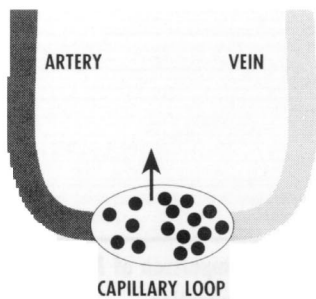


FIGURE 2 - Differences in pressure govern the exchange of fluid between the intravascular and interstitial fluid compartments. At the arterial side, the higher hydrostatic pressure forces fluid through the permeable capillary walls. This increases the protein (circles) concentration, increasing oncotic pressure. When the blood reaches the venous end, the low hydrostatic pressure and high oncotic pressure draw water back into the vessels. An increase in venous hydrostatic pressure or decrease in plasma proteins increases fluid in the interstitial space; this is termed **edema**.

Interchange of water between compartments

Osmotic pressure, caused by a difference in the number of proteins and electrolytes on either side of the membranes of cells, is the **most important** factor regulating movement of water back and forth between the intracellular space and the intravascular space.

Hydrostatic pressure drives fluid from the vessels at the arterial end of the capillary bed. The resultant loss of fluid from the vascular space increases the concentration of proteins, and increases tissue hydrostatic pressure. At the venous end of the capillary bed, therefore, hydrostatic pressure in the interstitial space is slightly higher than venous pressure, and venous **colloid oncotic pressure** from proteins exerts an additional osmotic effect, drawing water back into the vascular space. The combination of low venous hydrostatic pressure and high capillary oncotic pressure is important in controlling the balance of fluid between the intravascular space and the interstitial fluid, as shown in **Figure 2**.

PHYSIOLOGIC RESPONSE TO ALTERED PLASMA OSMOLALITY

Each day, there is a loss of about 2-3 liters of water from the body. Most of this water is lost in urine, although the amount excreted there is able to change to meet variations in water intake. An average of 1 liter/day of water is lost in sweat, stool, and through respiration (**insensible fluid losses**). Water must be taken in to replace these losses, or dehydration will result. The body has a complex regulatory

system which, under most circumstances, matches water intake with losses and prevents changes in osmolality or volume of plasma.

Osmoregulators

The **hypothalamus** (a regulatory center at the base of the brain) responds to an increase in osmolality (usually representing an increase in serum sodium) of less than 1%, activating two types of protective responses.

Thirst sensors respond to an increase in osmotic pressure, increasing water intake, lowering osmolality, and returning the system to normal. To a much lesser degree, thirst receptors respond to a decrease in intravascular volume. Intake of water triggered by thirst is the most important factor in maintenance of normal water and electrolyte status. Patients with neurologic disorders, the elderly, newborns, and those without access to water (including infants) often cannot respond to this signal; thus, they are prone to dehydration.

Antidiuretic hormone (ADH). The hypothalamus also produces this hormone in response to an increase in osmolality. ADH causes an increase in permeability of the collecting ducts of the kidney to water, increasing urine osmolality and attempting to return plasma osmolality to normal. While ADH can decrease water loss in the urine, it can only reduce total water losses from the body to a minimum of about 1 - 1.5 liters daily.

| Factor | Stimulus | Effect |
|---|--|---|
| Thirst | Increase in osmolality of 1%; decrease in volume > 5% | Increase water intake; decrease osmolality |
| Antidiuretic Hormone (ADH) | Increase in osmolality of 1%; decrease in volume > 5% | Increase water reabsorption by kidney, sweat glands; decrease osmolality |
| Renin/angiotensin/aldosterone | Decrease in volume; decreased electrolyte in urine | Increase blood pressure; increase serum Na (slightly), decrease serum K, H; decrease urine Na, increase urine K, H |
| Atrial Natriuretic Hormone (ANH) | Increase in atrial blood volume | Increase urine Na, decrease blood volume; decrease aldosterone |

Table 4 - Regulators of Osmolality and Volume

Volume regulators

While day to day regulation of water status is governed by osmolality, the body is able to override the signal of the osmoreceptors if necessary to preserve normal plasma volume. Volume regulators are relatively insensitive, compared to osmoreceptors, which are triggered by a change of 1% in plasma osmolality; however, they are also much more potent.

ADH. While changes in osmolality usually control ADH production, the hypothalamus also increases production of ADH whenever the volume of blood decreases by more than 5-10%, and produces a massive amount of ADH when the volume falls by more than 10-15%, even if plasma osmolality is decreased. Apparently, conservation of an adequate intravascular volume is more important than a normal plasma osmolality.

Renin-angiotensin-aldosterone system. With a decrease in renal blood flow or in the amount of sodium reaching the distal tubule, **renin** is released. Renin catalyzes production of angiotensin I and, indirectly, **angiotensin II (AG II)**. AG II is a potent vasoconstrictor, which serves to increase renal blood flow. Additionally, AG II is the most potent stimulus to **aldosterone**, which causes sodium retention in the distal convoluted tubule by exchanging sodium for potassium or H^+ . By this combined mechanism, renin increases renal blood flow by increasing total body sodium and arterial resistance.

Atrial natriuretic hormone (ANH). An increase in the amount of stretch of atrial myocardium stimulates ANH production. ANH appears to cause shunting of blood within the kidney to more cortical nephrons, decreasing maximum sodium reabsorption. In addition, ANH inhibits adrenal production of aldosterone. These two effects tend to decrease plasma volume and total body sodium.

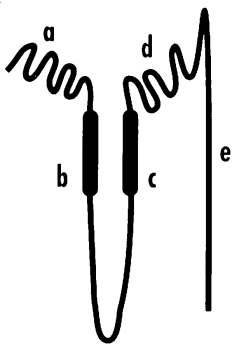


FIGURE 3 - The renal tubule has several segments which control water and solute status. Initially, the proximal convoluted tubule (a) absorbs most solutes, about 2/3 of sodium and water, and chloride. In the first half of the loop of Henle (b), water is absorbed in excess of sodium, increasing osmolality to as much as 1200 mosm/kg. In the next segment (c), sodium and chloride absorption produces a fluid with a relatively low osmolality and virtually no potassium. The distal convoluted tubule (d) can absorb sodium in exchange for potassium or hydrogen ion, mainly under the effects of aldosterone. The collecting duct (e) can, in the presence of ADH, absorb water and produce a very concentrated urine.

RENAL REGULATION OF WATER AND SOLUTE CONCENTRATIONS

Since the action of many of the hormones is primarily on the kidney, normal renal function is essential to maintenance of normal water and electrolyte status. Because glomerular filtration, the first step in renal excretion, is a non-selective process, substances vital to the body are passed into the urine. In a normal person, approximately 180 liters of water and 25,000 mmol of sodium enter the urine each day! It is the function of the tubules of the kidney to adjust the excretion of water and electrolytes to maintain normal volume status. In the normal kidney, most of the reabsorption of sodium, chloride, and water takes place by simple diffusion against an osmotic gradient; this requires that there be no disease in the kidney which alters the very high osmolality found in the central portion of the kidney. The final adjustment of urine electrolyte and water is accomplished through the action of aldosterone and antidiuretic hormone. In the absence of aldosterone, approximately 3-5% of the sodium reaching the urine can be lost in the urine, while ADH deficiency may allow as much as 10% of water to be excreted. This is illustrated in Figure 3.

“Normal” Values for Urine Solute Concentration

While the laboratory is frequently asked to define “normal” values for urine solute concentrations and osmolality, the function of the kidney is best understood in terms of “appropriate” values. For example, if a patient is dehydrated, an extremely dilute urine with an osmolality of 50 is inappropriate, even though such a value could be found in a healthy person. Similarly, a urine sodium concentration of 100 mmol/L in the same patient would also be inappropriate. In our own laboratory, we do not publish reference values for urine osmolality or electrolyte concentrations.

Concentration and Dilution

The kidney is capable of excreting urine of varying concentrations through the action of the renal tubules. In states of water deprivation, ADH stimulates maximal water conservation, such that urine may achieve an osmolality as high as 1200 mosm/kg. With excessive water intake, maximal dilution can produce an osmolality as low as 50 mosm/kg. In childhood and with increasing age, these values differ; those over 65 often cannot achieve maximum concentrations over 700 mosm/kg, while maximal diluting ability is often no lower than 100-150 mosm/kg.

Urine Electrolytes

In health, urine electrolyte excretion is related to salt intake; in fact, total urine sodium excretion in healthy individuals is a good marker of dietary sodium, and has been advocated as a tool for monitoring salt intake in patients with high blood pressure. With a change in plasma volume, however, hormones stimulate the kidney to alter sodium excretion to reestablish the normal state. In a patient with volume depletion, aldosterone, acting on the renal tubules, can reduce urine sodium losses to less than 0.5% of the amount filtered by the glomerulus; urine sodium concentrations are typically less than 10 mmol/L. With volume overload, urine sodium excretion increases dramatically, and may reach 5% or greater of filtered sodium, with sodium concentrations in excess of serum sodium concentration by 2 or more times.

OSMOTIC GAP

Osmotic gap is a theoretical concept (similar to the anion gap) introduced initially as a check on the accuracy of instruments for measuring osmolality. The osmotic gap is defined as the difference between the actual, measured osmolality, and that calculated from the molal concentrations of all major solutes present in serum. Two commonly used formulas for calculated osmolality are given as equations 1 and 2.

Equation 1

$$\frac{1.86 \times \text{Na}^+ + \frac{\text{Glucose}}{18} + \frac{\text{BUN}}{2.8} + \frac{\text{Ethanol}}{3.8}}{0.93}$$

Equation 2

$$2 \times \text{Na}^+ + \frac{\text{Glucose}}{18} + \frac{\text{BUN}}{2.8} + \frac{\text{Ethanol}}{3.8}$$

Only about 93% of serum is actually water, the rest representing lipid and protein suspended in water. Osmotically active substances are dissolved in **water**, not **plasma**; since only 93% of plasma is water, the resulting values are all divided by 0.93; thus, 1.86 x Na becomes 2 x Na, and so forth. The conversion factors for glucose and urea convert concentration from mg/dL to mmol/L. While the expected conversion factor for ethanol would be 4.6, ethanol does not act only as a solute; it also is a solvent. The conversion factor of 3.8 was empirically determined from the observed effects of alcohol in solution. Osmotic gap can be up to 10; the difference occurs because there are small amounts of other osmotically active substances, such as potassium, which are not included in either formula.

An osmotic gap indicates the presence of a small molecular weight compound in millimole amounts. For all practical purposes, the only substances which can produce an osmotic gap are alcohols (methanol, isopropanol, ethylene glycol, and propylene glycol), acetone, acetylsalicylic acid, and paraldehyde. Ethanol will cause an osmotic gap if it is not routinely measured and included in formulas for calculated osmolality as suggested above. Only non-ionized substances will contribute to an osmotic gap; for example, acids dissociate to produce a conjugate base which directly replaces HCO_3^- ; since we have accounted for anions by multiplying Na by 2, an increase in an "unmeasured" anion will not cause an osmotic gap. The method used to measure osmolality will influence whether an osmotic gap is present. Since most of the substances which can cause a gap are volatile (except for aspirin), osmometers which measure decrease in vapor pressure will not detect their presence. Fortunately, the majority of hospital laboratories in this country measure osmolality by freezing point depression, which accurately measures the presence of all osmotically active substances.

FREE WATER CLEARANCE

Free water clearance is a theoretical concept, evaluating the ability of the kidney to excrete more (or less) water than is necessary to handle the osmotic load filtered by the glomerulus. This reflects the ability of the tubules to concentrate and dilute urine as necessary to adjust to changes in volume status of the patient. Free water clearance is calculated as the difference between **total** water clearance (urine volume) and **required** water clearance (osmolar clearance), as defined by the following formula:

$$C_{H_2O} = C_{urine} - C_{osm} = V - \frac{U_{osm} \times V}{P_{osm}} = V \times \left(1 - \frac{U_{osm}}{P_{osm}} \right)$$

If the kidney has no **net** reabsorption of water, but excretes urine with the same osmolality as plasma, then free water clearance is zero. In states in which there is decreased blood volume, an appropriate response is to increase production of antidiuretic hormone, causing excretion of a concentrated urine with proportionally less water than serum; free water clearance is thus negative. Similarly, ingestion of increased water depresses ADH production and causes excretion of a very dilute urine, and free water clearance is positive. If all steps in the regulatory system and the kidneys are functioning properly, urinary solute concentration will be appropriate for the fluid status of the body.

Measurement of osmolality is a simple and relatively inexpensive procedure; the commonly asked question relates to its clinical usefulness. The following section details the major uses of measurements of osmolality, some of which will be illustrated by case studies later in the handout.

Clinical Uses of Serum Osmolality

Screening for Toxin Ingestion (Osmotic Gap = Molar Concentration of Solute)

- ◆ Alcohols (Methanol, Isopropanol)
- ◆ Glycols (Ethylene, Propylene)

Monitoring Concentration of Osmotically Active Agents

- ◆ Mannitol

Evaluation of Hyponatremia

- ◆ Exclusion of pseudohyponatremia
- ◆ Presence of other osmotic agents (glycine, glucose)

SCREENING FOR TOXIN INGESTION

Probably the single most useful application of osmolality is in the evaluation of patients suspected of having ingested a toxin. If the poison is present in millimolar concentrations, then osmolality (using freezing point depression for all uncharged toxins or vapor pressure osmometry for non-volatile toxins) will be increased. Calculating the *osmolal gap* as the difference between measured and calculated osmolality (as presented in Equations 1 and 2) gives a reliable estimate of the molar concentration of any additional substances present. Among those toxins which can be detected by osmolality are the alcohols methanol, ethanol, and isopropanol; ethylene and propylene glycol; salicylic acid (aspirin and related compounds); and paraldehyde. If the compound can be identified by qualitative methods, then the concentration in mg/dL can also be calculated by multiplying the osmolal gap by the factor (molecular weight/10).

MONITORING THE CONCENTRATION OF OSMOTICALLY ACTIVE AGENTS

In the treatment of patients with cerebral edema (swelling of the brain), osmotically active compounds such as mannitol are often given in an attempt to draw water out of cells, reducing the amount of edema present. Because there is no easy way to determine the concentration of mannitol, some have suggested using the osmotic

gap as a way to estimate mannitol concentration. The goal of therapy is to maintain an *increase* in osmotic gap of 10 mosm/kg. This illustrates the necessity of selecting methods with good precision for measuring osmolality and electrolytes. If osmotic gap reaches 50 mosm/kg, renal damage from mannitol is likely.

EVALUATION OF HYPONATREMIA

Because sodium (along with its associated anions) is the major contributor to serum osmolality, most patients with hyponatremia also have decreased serum osmolality. Occasionally, a low serum sodium is not associated with hypoosmolality. This most frequently occurs in patients with an increased serum glucose, since glucose is capable of forcing water to leave the intracellular fluid, diluting serum electrolytes. Patients with diabetes usually have increased osmolality, with occasional patients falling in the normal range. A rough estimate is that, for every 100 mg/dL increase in glucose, sodium concentration should fall by between 1.6-2.0 mmol/L. Because this increases osmolality 5.6 mosmol/kg (for glucose) while decreasing it 3.2-4.0 (for sodium), it follows that osmolality will increase 1.5-2.5 mosm/kg for each 100 mg/dL increase in sodium. A greater increase implies significant loss of water relative to sodium or the presence of other osmotically active molecules; a lower increase implies excess sodium loss.

Other osmotically active substances, such as mannitol (mentioned above) and glycine may produce the same phenomenon, though with a normal serum osmolality. Glycine is used by urologists in irrigation fluids employed to provide a clear field of vision while performing a TURP (transurethral resection of the prostate). Because the fluid is infused under pressure, some of it can be absorbed into the circulation if the surgeon cuts through a venous sinus (which are abundant in the prostate). In about 5-10% of cases, enough fluid is absorbed to significantly dilute the serum sodium; while this is innocuous, the increased fluid and the glycine may cause other problems for the patient. The magnitude of fluid absorbed and the rate of metabolism of glycine can be estimated from the osmolal gap.

Finally, because most methods for sodium measure concentration in *plasma* rather than in *water* (which is what is regulated by osmoreceptors), patients whose water content of plasma is lower than normal will have falsely low serum sodium. This phenomenon occurs in the presence of markedly increased total protein or lipids if sodium is measured by flame photometry or ion selective electrodes using diluted

specimens (most instruments). Since osmolality is related to solute concentration in water, such patients will also have a normal osmolality.

URINE OSMOLALITY

Because osmolality is the most accurate measurement of total solute concentration, it provides the best estimate of the kidney's concentrating ability. This is essential in the evaluation of alteration in renal function. Urine osmolality is a measure of total urine solute, which normally is composed primarily of waste products such as creatinine and urea (approximately 80% of total solute in normal urine). In patients with kidney disease, electrolytes may make up an increasing percentage of total solute, while persons with very high blood levels of other solutes (glucose, ethanol) may have over 30% of urine solute composed of this substance. For this reason, urine osmolality is usually interpreted along with measures of urine electrolytes and creatinine.

Uses of Urine Osmolality

Evaluation of Increased Urine Output

- ◆ Primary polydipsia (low serum, low urine osmolality)
- ◆ Diabetes insipidus (high serum, low urine osmolality)
- ◆ Diabetes mellitus (high serum, high urine osmolality)

Evaluation of Decreased Urine Output

- ◆ Dehydration (high urine osmolality, negative free water clearance)
- ◆ Acute tubular injury (0 free water clearance)

Evaluation of Renal Acidification Defects

- ◆ Urine osmolar gap = NH_4^+ excretion

Increased Urine Output

In most patients, increased urine output is caused by one of three major causes. Most commonly, it is due to an increased ingestion of water, termed *polydipsia*. This may be due to a compulsion to drink water because of a psychiatric disorder (psychogenic polydipsia) or due to a perception of thirst because of a dry mouth or in an attempt to cure hiccups (primary polydipsia). In both types of polydipsia, the urine osmolality will be at maximal diluting capacity, which is typically below 100 mosm/kg.

Increased water ingestion may also occur due to absence of ADH (central diabetes insipidus) or inability of the kidney to respond to ADH (nephrogenic dia-

betes insipidus, often due to medications such as lithium). In both of these states, the urine osmolality will also be markedly decreased; however, serum osmolality will be slightly increased in diabetes insipidus while it is decreased in polydipsia. Traditional teaching describes use of a "water deprivation" test to evaluate such patients; in theory, normal individuals will respond with a rapid increase in urine osmolality to > 300 mosm/kg, while patients with diabetes insipidus will not respond. Differentiation of central from nephrogenic diabetes insipidus is made by demonstrating an increase in urine osmolality with ADH administration in the latter group. In practice, prolonged high urine output impairs the kidney's ability to maximally respond to ADH, so that results are often similar in both groups. Repeating the test after correcting increased urine output (with ADH if necessary) gives more easily-interpreted results.

In patients with diabetes mellitus, the increased concentration of glucose in the urine causes increased loss of water; such patients typically have increased urine and serum osmolality.

Decreased Urine Output

A fall in urine production may be due to intrinsic kidney problems or an appropriate attempt to conserve water and electrolytes. An acute decrease in urine output due to kidney disease is, in the majority of cases, due to acute damage to the tubules of the kidney (acute tubular necrosis, ATN, death of tubular cells due to drugs, poisons, or decreased blood flow; or interstitial nephritis, an inflammation usually due to a drug).

With tubular injury, the osmolality of the urine approaches that of plasma (approximately 290 mosm/kg), and free water clearance approaches zero. While many textbooks of both medicine and clinical pathology discuss measurement of urine electrolytes and fractional excretion of sodium, free water clearance has been shown to become abnormal an average of a day earlier than sodium measurements in patients with ATN. In practice, sodium excretion often remains low for 2-3 days following onset of ATN.

If decreased urine output is due to decreased blood flow to the kidneys, they will appropriately attempt to conserve water and sodium to try to minimize further decreases in blood flow. In this situation, the urine osmolality will be extremely high. (In practice, sodium excretion often remains low for 2-3 days following onset of ATN.)

Evaluation of urine osmolality and electrolytes is also helpful in evaluating patients with suspected inappropriate ADH production. Such patients tend to have high urine osmolality which does not rise appreciably with fluid restriction or fall with fluid administration. Such dynamic testing is often necessary to establish the diagnosis.

Evaluation of Urine Acidification

Normally, the main form of acid excreted by the kidney is NH_4^+ . In some cases of kidney disease, there is an inability of the kidney to maximally excrete acid or reabsorb bicarbonate; these defects are collectively referred to as *renal tubular acidosis*. Patients with these defects tend to have a reduction in ammonium ion excretion. Since this is difficult to measure directly, several indirect approaches to ammonium measurement have been suggested. The one which seems to be the most accurate is the urine osmotic gap, defined as:

$$\text{Osmolality}_{\text{measured}} \left[2 \times (\text{Na}^+ + \text{K}^+) + \frac{\text{Urea}}{2.8} + \frac{\text{Glucose}}{18} \right]$$

STOOL OSMOLALITY

Occasionally, measurement of osmolality in stool is helpful in evaluation of patients with diarrhea. In normal stool, most small molecular weight substances are totally absorbed (except for electrolytes); thus, most of the osmotic activity of stool comes from electrolytes. A stool osmotic gap has been defined as the difference between the measured osmolality and a calculated osmolality (determined as two times the sum of Na and K ions in stool) or, more accurately, serum osmolality.

Uses of Stool Osmolality

Separation of Secretory from Osmotic Diarrhea

Osmotic Diarrhea

- ◆ Presence of unabsorbed solutes
- ◆ Due to laxative abuse, malabsorption

Secretory Diarrhea

- ◆ Due to agents damaging mucosa (inflammation, infections, drugs such as phenolphthalein)

In most cases of diarrhea, the disease is due to an infection or to a bacterial toxin, and the diarrhea resolves in a short period of time. Stool osmolality is of little use in such patients. If diarrhea persists for more than a week and if cultures are negative, the cause of diarrhea may be more difficult to discern. Gastroenterologists have described two major forms of diarrhea: osmotic and secretory. In osmotic diarrhea,

there is some unabsorbed substance in the stool which prevents normal absorption of water (for example, this is how most laxatives work). In such patients, the osmotic gap is typically over 50 mosm/kg. An osmotic diarrhea is seen in patients who ingest excess laxatives, and also in cases of malabsorption of nutrients.

If there is intrinsic damage to the intestinal mucosa such that it cannot absorb water and electrolytes, then a "secretory" diarrhea occurs. This is common in patients with mechanical disease of the intestine, such as inflammation, tumors, and decreased blood flow.

An important consideration in measuring stool osmolality is that bacterial metabolism produces osmotically active substances; measurements must be made within 30 minutes of collection of a specimen, or the specimen should be refrigerated until analysis is to be performed.

CASE A—POSSIBLE TOXIN INGESTION

A 43 year old white male with a history of depression and alcohol abuse was found lethargic on the floor of his room by his family. He was brought to the emergency room, where he was found to be confused; he became comatose over the next hour. Laboratory results in the emergency room included Glucose 115 mg/dL, BUN 9 mg/dL, Na 145 mmol/L, K 4.2 mmol/L, Cl 112 mmol/L, and CO₂ 7 mmol/L. Serum osmolality was 383 mosm/kg. Blood ethanol was negative. Arterial blood gas analysis: pH 7.12, pCO₂ 34 mm Hg. A serum for volatiles was negative, as was a urine Toxi-Lab screen. Calculate serum osmolality and osmotic gap. What is the significance of the serum osmolality in view of the negative screen for serum volatiles, negative blood ethanol, and negative urine Toxi-Lab?

Discussion

Initial laboratory results indicate the presence of an anion gap of 26 mmol/L, and an osmotic gap of over 80, not explained by ethanol. The differential diagnosis of such a case is relatively limited, and the clinical picture of intoxication progressing to coma limits the differential even further, suggesting the possibility of ingestion of an alcohol or glycol. Volatile screens, performed by head space gas chromatography of blood, measure precisely what their name implies: volatile compounds. This includes ketones and alcohols, but typically will not detect the minimally volatile glycols. Similarly, Toxi-Lab screens for the presence of substances extractable with non-polar solvents; highly polar compounds, such as alcohols, glycols, and opiate glucuronides are not detected by this method in most cases. It is vital for the laboratory to be provided with all information about suspected toxins, since even a complete "screen" using head space chromatography and GC-mass spectrometry of plasma and urine extracts will miss certain compounds such as heavy metals and glycols. In this case, the prompt determination of osmolality led to the suspicion of poisoning with ethylene or propylene glycol or methanol, even before the results of the volatile or Toxi-Lab screens had been reported.

A few ancillary tests which are often available in most laboratories can help to narrow this differential diagnosis further. Propylene glycol toxicity most commonly occurs in hospitalized patients with renal insufficiency, since the chemical is used as a solvent for many drugs and is normally excreted in the urine. Occasional cases of poisoning occur from exposure in food or from unknown sources. Lactate is the major metabolite of propylene glycol, and will be markedly increased in cases of

poisoning. Ethylene glycol is found in antifreeze, and is usually taken as an intentional overdose; however, sometimes it contaminates illicit "moonshine" liquor. It is metabolized to glyoxalate and oxalate. Urine was requested for examination for calcium oxalate crystals. A moderate number of calcium oxalate monohydrate crystals were present; these ovoid crystals, as compared with the more typical square "envelope" calcium oxalate dihydrate crystals, are quite characteristic of ethylene glycol intoxication. A specimen was obtained for ethylene glycol assay, and the patient was begun on an ethanol drip, bicarbonate was administered, and dialysis was begun (the standard treatment for poisoning with any of these compounds). About four hours later, the patient regained consciousness and confirmed that he had ingested Prestone antifreeze in an attempt to get drunk, since the family had taken all of the alcohol out of the house before his visit. About three hours later, the result of the ethylene glycol level was available; the concentration was 500 mg/dL, well above the potentially fatal level. Dialysis was continued over the next 12 hours, until his osmotic gap fell to zero.

In this case, osmolality both assisted in the diagnosis and provided a guide to management of this patient. Prompt suspicion of the diagnosis led to appropriate treatment; the patient recovered completely, never developing any evidence of renal, pulmonary, or cardiac damage, and he was discharged three days later. Because osmolality is available rapidly, it is the quickest and best screening test available for ingestion of these possibly deadly poisons.

CASE B—EVALUATION OF HYPONATREMIA

The supervisor in the stat laboratory noticed that the results on a patient in the operating room had changed significantly since the previous evening, as shown in the accompanying table. A repeat specimen gave the same results as that from the second specimen received, while a specimen from two days before agreed with the first specimen. Estimate the calculated osmolality and osmotic gap. What are the possible causes for these findings?

| TIME | Na | K | Cl | CO ₂ | BUN | Creatinine | Glucose | Osmolality |
|------------|-----|-----|-----|-----------------|-----|------------|---------|------------|
| 2/17, 6 pm | 143 | 5.6 | 111 | 17 | 20 | 1.6 | 111 | 294 |
| 2/18, 3 pm | 112 | 4.7 | 93 | 16 | 16 | 1.3 | 150 | 280 |

Discussion

In this case, there are several considerations. Comparing the results of the second specimen with the first, there is clearly a significant difference in sodium, chloride, and anion gap (anion gap was 15 in the first specimen but only 3 in the second specimen); healthy persons show little variation in these from day to day. There is a large osmotic gap of 42 in the second specimen but a gap of essentially zero in the first specimen. The relatively normal osmolality in the presence of a low sodium suggests the possibility of a specimen containing increased solids, such as protein or lipids. The specimen was not lipemic and preoperative serum protein and albumin were normal. Since excess protein is not administered to patients, these causes can be excluded. Additionally, the slightly lower osmolality indicates some change in total solute, which would not occur with altered protein or lipid. A second possibility is that the two specimens came from different individuals; however, two specimens on the day before surgery from this patient gave the same results, and a second specimen from the operating room had a sodium of 109. The third and, now, most likely, possibility is that the patient has received a hypotonic solution of a drug which is both osmotically active (diluting sodium and lowering osmolality slightly) and an unmeasured cation (lowering the anion gap). While several drugs such as mannitol are osmotically active, few are positively charged. The major candidate likely to cause this picture is the amino acid glycine.

Glycine solutions with relatively high osmolality (between 200 and 220) are commonly used as irrigation fluids during surgical resection of tissue from the bladder, prostate, or uterus. Such procedures are done using electrical cautery with visual

inspection; washing the surface is necessary to allow the surgeon to visualize the abnormal tissue and prevent injury to normal tissues. Because the fluid must be infused into the organ under pressure, it could be absorbed through opened blood vessels. Water cannot be used, since its absorption would markedly lower osmolality and could cause hemolysis. Electrolyte solutions such as normal saline cannot be used because they conduct and diffuse electricity. For these reasons, glycine solutions have become the preferred irrigation fluid.

While removal of the lining of the uterus has been associated with absorption of small amounts of glycine, severe hyponatremia from glycine absorption usually occurs during TURP. In resecting the prostate, upwards of 60 liters of irrigation fluid can be used. If the surgeon accidentally cuts into a venous sinus (a large blood vessel in the prostate), many liters of fluid can be absorbed. While the patient is hyponatremic, this does not cause problems in itself, since osmolality is relatively normal. The large amount of fluid can cause edema of the lungs and can impair heart function. The glycine can, either by itself or through generation of ammonia, alter brain function and can even produce coma in cases of extensive absorption. The fall in the sodium provides evidence of the amount of fluid absorbed.

Between 5 and 10% of patients undergoing TURP absorb enough fluid to lower their serum sodium below 125. An osmotic gap proves the presence of glycine, and can be used after surgery to determine the rate of its clearance.

CASE C—EVALUATION OF HYPONATREMIA

A 32 year old male presented with a history of one episode of passing blood in his stool. He had a history of alcohol abuse, and had been in an automobile accident the previous year, injuring his head. After routine laboratory tests revealed a serum sodium of 115 mmol/L, he was questioned further, and stated that he is "always thirsty" and drinks several glasses of water daily to help with this. What is the likely cause for hyponatremia? One of the physicians questioned whether he might have either diabetes insipidus or inappropriate ADH production; can these results help determine the likelihood of either diagnosis?

| SPECIMEN | Na | K | Cl | CO ₂ | BUN | Creatinine | Glucose | Osmolality |
|----------|------|-----|------|-----------------|-----|------------|---------|------------|
| Serum | 115 | 4.8 | 79 | 26 | 3 | 0.7 | 84 | 246 |
| Urine | < 10 | 6.3 | < 15 | | | 14.1 | | 44 |

Discussion

In this case, the patient has marked hyponatremia and hypochloremia with a markedly low BUN and lowered osmolality. These findings suggest the presence of water overload, either due to inappropriate antidiuretic hormone production or overingestion of water. Diabetes insipidus can cause a low urine osmolality and high urine output and cause the patient to be chronically thirsty; however, thirst is driven by an increased osmolality, while this patient's serum osmolality is markedly decreased. The combination of diluted serum with a urine showing maximal dilution firmly establishes the diagnosis of water intoxication. This patient was treated with water restriction, and by 24 hours later his serum sodium had increased to 133 and his urine osmolality had risen to 223; he was discharged from the hospital. Primary polydypsia, as was present in this case, is a relatively common disorder; we see 5-10 patients a year with this phenomenon. In my experience, this is much more frequent than compulsive water drinking in psychiatric patients, which has been much more widely reported. Most patients respond quickly to fluid restriction; however, many of our patients have been admitted on more than one occasion with the same problem, suggesting that there may indeed be some component of psychiatric compulsion to drink water.

CASE D—EVALUATION OF HYPONATREMIA

The evening supervisor notes that a patient's serum sodium has failed delta check alerts compared to the results from the previous week. She had run the initial specimen on the Beckman CX-7, and repeated the test on the Ektachem. All results were similar except for the sodium. The specimen was retested on both instruments and the results were essentially the same as the first determination on each instrument. Several other patients were run, and there were no differences in results between the CX-7 and the Ektachem. Serum osmolality was measured as 302. What is the osmotic gap using results from each of the two instruments? What is the cause for the discrepancy of results from the two specimens? Does this patient have an abnormality of sodium?

| INSTRUMENT | Na | K | Cl | CO ₂ | BUN | Creatinine | Glucose |
|------------|-----|-----|-----|-----------------|-----|------------|---------|
| CX-7 | 129 | 5.0 | 107 | 19 | 33 | 2.0 | 152 |
| Ektachem | 142 | 5.1 | 107 | 20 | 33 | 2.1 | 155 |

Discussion

As with case B, this patient had results which differed significantly from a previous specimen on the same patient. In this case, however, there is a discrepancy between two different instruments measuring the same analyte. On the CX-7, sodium is measured by ion selective electrodes (ISE's) using diluted samples; on the Ektachem, non-diluted ISE's are employed. There is an osmotic gap of 24 using the results from the CX-7, while there is a gap of -2 using the Ektachem results. Since the Ektachem showed the higher sodium value, the most likely explanation is that the patient's serum had increased solids. Since it was not lipemic, an increase in protein was the most likely etiology; the patient turned out to have multiple myeloma with a total protein of 13.8 g/dL.

Because lipemia is the most common cause of this phenomenon, many laboratories routinely clear specimens of gross lipemia before performing analyses for electrolytes if using diluted ISE's or flame photometry. This patient's "serum" sodium is actually low, since each mL of serum actually contains only about 86% water. However, the concentration of sodium in plasma water was actually normal, as reflected by the normal serum osmolality. Since the body regulates the concentration of sodium in water, this patient has no abnormality of sodium metabolism.

CASE E—EVALUATION OF HYPONATREMIA

A 74 year old man was admitted in February with a stroke. After about one month in the hospital, he developed shortness of breath and was found to have pneumonia, which was resistant to treatment, raising the possibility of an ongoing source. His intake of food was limited, and he was maintained on intravenous fluids until about the beginning of March when a feeding tube was inserted. He was noted to be hyponatremic at this time, and his serum sodium did not increase despite addition of extra salt to his tube feedings. What do the urine and serum osmolalities reveal? What is the most likely etiology for these findings?

| SPECIMEN | Na | K | Cl | CO ₂ | BUN | Creatinine | Glucose | Osmolality |
|------------|-----|------|----|-----------------|-----|------------|---------|------------|
| Early Feb. | 138 | 3.6 | 98 | 25 | 17 | 0.9 | 143 | |
| Early Mar. | 120 | 4.6 | 83 | 23 | 15 | 0.5 | 131 | 257 |
| Late Mar. | 113 | 4.9 | 81 | 21 | 9 | 0.7 | 89 | 239 |
| Urine | 70 | 70.1 | 41 | | | 90.7 | | 694 |

Discussion

His serum osmolality was low, confirming that there is a true sodium abnormality present. His urine osmolality indicates a specimen that is significantly concentrated compared to serum, indicating the presence of ADH activity.

In evaluating a patient with ADH production, the first step is to determine whether it is being produced appropriately. Because the major stimulus to ADH release is increased plasma osmolality, hypoosmolar patients would be expected to produce the hormone only if they had a decrease in intravascular volume. Physicians often look for evidence of an abnormal blood pressure change when the patient stands up as an indicator for decrease in blood volume; however, this is not present until there has been a decrease of at least 5-10% in total volume. The ratio of BUN to creatinine increases with volume depletion, since urea is reabsorbed from urine along with water in cases of dehydration (causing a selective decrease in urea clearance and an alteration of the normal BUN/creatinine ratio).

From the time of admission, this patient's serum BUN and creatinine gradually decreased with a lowering of the BUN/creatinine ratio. This pattern is most frequently seen in patients who have water overload, as discussed in case C above. The combination of hyponatremia, decreased BUN and creatinine with low ratio, and evidence of ADH production without appropriate stimulation are thus diag-

nostic of the syndrome of inappropriate antidiuretic hormone (SIADH) production. This disorder is an extremely common cause of hyponatremia in hospitalized patients. The most common causes are diseases of the lung and brain; a large number of different illnesses affecting these organs can cause this syndrome. In addition, cancers are often associated with SIADH.

In this patient, there are two likely causes for this illness, pneumonia and the initial stroke. Salt administration is usually ineffective in treating patients with SIADH, since the expansion in their vascular volume stimulates ANH production, increasing urinary sodium losses. For mild cases of SIADH, restriction of water intake often is adequate in controlling the hyponatremia. In more severe cases, as in this patient, or if the syndrome is due to a malignancy, it is often necessary to use a drug which antagonizes the effects of ADH on the kidney; the most widely used agent is the antibiotic, demeclocycline, which was used in this patient when he did not respond to fluid restriction.

CASE F—EVALUATION OF HIGH URINE OUTPUT

A 54 year old man is hospitalized on the psychiatry service for treatment of manic-depressive disorder; he is currently receiving lithium carbonate treatment. He states that he is always thirsty, and he has a daily urine output of over 8 liters per day. A consult is placed to the endocrinologists to rule out nephrogenic diabetes insipidus, and they call the laboratory to ask for help in interpreting the accompanying results. What would be the most likely reasons for a high urine output? Which of them have low urine osmolality? What is the most likely cause in this case?

| SPECIMEN | Na | K | Cl | CO ₂ | BUN | Creatinine | Glucose | Osmolality |
|----------|------|-----|------|-----------------|-----|------------|---------|------------|
| Serum | 126 | 3.0 | 92 | 25 | 10 | 1.1 | 145 | 269 |
| Urine | < 10 | 3.5 | < 15 | | | 31.7 | | 53 |

The laboratory results in this case are very similar to those in case C, and, in fact, this is another example of water intoxication, this case due to psychogenic compulsion to drink water.

In this case, the initial evaluation was based on a difference in urine output rather than the decreased serum sodium. Increased urine output is usually due to one of two major disorders: water intoxication or diabetes insipidus. In both of these disorders, urine osmolality is low, since ADH production or response is decreased in both. In water intoxication, as in this case, ADH production is appropriately decreased by decreased plasma osmolality; in this case, thirst is an inappropriate response, since volume status is normal. In diabetes insipidus, ADH is either absent (central diabetes insipidus) or ineffective (nephrogenic diabetes insipidus). Lithium can produce nephrogenic diabetes insipidus, which was the concern of the psychiatrists in this case.

In this patient, simple water restriction led to resolution of the hyponatremia and lowered the urine output. In many cases, however, the diagnosis is not as easy to determine. Prolonged water ingestion tends to reduce the high concentration in the kidney which is needed to produce maximal urine concentration. If this has occurred, then cessation of water ingestion may not immediately decrease urine output, and the patient may become dehydrated. In such a case, the diagnosis of diabetes insipidus is often made, and the patient is required to take ADH indefinitely. It is often advisable, particularly if the serum sodium is initially low (as in this case) to repeat the results after a period of water restriction (using ADH therapy, if necessary).

CASE G—EVALUATION OF HIGH URINE OUTPUT

A 36 year old man with a history of alcohol abuse was admitted for evaluation of seizures. On the evening following admission, he fell, hitting his head. While the wound was being sutured, he became less responsive and lapsed into a coma. He was taken to the operating room for treatment, but did not regain consciousness as of when these results were observed late in the evening after surgery. His urine output had averaged 800 cc per hour in the three hours after surgery. What is the significance of the urine osmolality in this case? What is the most likely diagnosis? Assuming your diagnosis is correct, how would you use urine osmolality to monitor treatment in this patient?

| SPECIMEN | Na | K | Cl | CO ₂ | BUN | Creatinine | Glucose | Osmolality |
|-----------|-----|-----|-----|-----------------|-----|------------|---------|------------|
| Admission | 137 | 4.2 | 103 | 25 | 15 | | 94 | |
| Next a.m. | 155 | 4.3 | 116 | 26 | 17 | 1.1 | 95 | |
| Next p.m. | 172 | 4.6 | 132 | 27 | 19 | 1.2 | 112 | 353 |
| Urine | 32 | 9.0 | 15 | | | | | 105 |

As discussed in case F, increased urine output with a decreased urine osmolality is caused by one of only two disorders. In this case, psychogenic polydipsia can easily be eliminated from the list of possibilities, since this patient was comatose. Excess fluid administration during surgery could be raised as a possibility, but would not explain the increase in serum sodium and osmolality. The results in this case are virtually diagnostic for diabetes insipidus.

The history of head trauma is typical; about 30% of cases follow accidental brain injury. Therapy with ADH was begun, and frequent (every 2 hour) measurements of urine osmolality were used to both decide on an initial dosage of the drug and to monitor continued treatment of the patient, with the goal to keep the urine osmolality over 300 (as long as fluid was being administered to the patient) and to keep urine volume to less than 60 cc/hr. While diabetes insipidus due to trauma often resolves, in this patient it continued until the patient died about one month following this accident.

In a patient in whom the diagnosis is not as obvious as in this case, a water deprivation test is often performed. This can be dangerous, and careful monitoring of the patient to avoid severe dehydration is needed. Specimens for urine osmolality (or, in this case, specific gravity is often used) are obtained hourly. The test is discontinued if the urine osmolality rises above 500 or if the patient loses more than 3% of body weight without a rise in urine osmolality.

Some recognize a "partial diabetes insipidus" in which osmolality rises to 500 but not to maximal concentration. Since, as mentioned in the text, maximal concentrating ability can be affected by age and other renal disease, this may be difficult to diagnose. If failure of urine osmolality to rise is the cause for finishing the test, ADH may be administered to see if the kidneys can then respond. As mentioned in the discussion for case F, however, response to ADH may be difficult to interpret if the disorder has been present for a relatively long period of time.

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CASE H—EVALUATION OF DECREASED URINE OUTPUT

A 35 year old man with a history of alcohol abuse was admitted with loss of appetite and diarrhea; he also had a diagnosis of cirrhosis. He was begun on treatment with vancomycin because of a positive blood culture. By the fourth day on antibiotics, he was noted to have decrease in his urine output to less than 300 mL per day; urine electrolytes and osmolality were ordered. What is the differential diagnosis for a decrease in urine output? How do laboratory tests help in this case in deciding between the various causes?

| TIME | Na | K | Cl | CO2 | BUN | Creatinine | Glucose | Osmolality |
|---------------|-----|------|-----|-----|-----|------------|---------|------------|
| Admission | 136 | 3.3 | 103 | 28 | | 0.6 | 125 | n/a |
| 4 d later | 133 | 4.1 | 112 | 18 | 10 | 4.5 | 72 | 287 |
| Urine (day 4) | 10 | 22.5 | 19 | | | | | 187 |

In a patient with decreased urine output, the two major diagnoses considered are (1) decreased blood flow to the kidneys, often termed prerenal azotemia, and (2) acute damage to the tubules, usually due to acute damage to the tubules (usually “acute tubular necrosis”). In this case, the history would have been compatible with either diagnosis.

Cirrhosis often is associated with decreased blood flow to the outer part of the kidney where most glomeruli are found; this causes a decrease in kidney function called “hepatorenal syndrome”. In any case of prerenal azotemia, the kidneys attempt to regulate their blood flow by producing renin and, ultimately, aldosterone, which causes maximal sodium retention. The decreased blood volume causes production of ADH, producing a concentrated urine.

In acute tubular necrosis (ATN), however, the intrinsic damage to the tubules renders them incapable of responding to either hormone. Common causes of ATN are shock and exposure to drugs which damage the renal tubules, including aminoglycosides and drugs such as vancomycin. Typically, response to ADH is lost first, reducing free water clearance to zero and resulting in production of urine with an osmolality near that of serum. Sodium excretion typically rises within about 24 hours, due to the lack of proximal tubular sodium reabsorption. If aldosterone had been increased before this event takes place, the increased distal tubular sodium reabsorption may cause urine sodium excretion to be low for as long as 48-72 hours.

At the time of initial investigation, the low urine sodium excretion suggested the diagnosis of prerenal azotemia to the physicians. However, the low free water clearance in this case implied the presence of acute tubular necrosis. By the next day, urine output remained low but urine sodium excretion increased. The patient continued to have low urine output, and he ultimately required hemodialysis for a period of approximately 1 month before his renal function improved enough that he no longer needed to be dialyzed. His renal function never returned to normal. This case illustrates the importance of free water clearance as an early indicator of ATN.

cases of acute
renal failure
with low urine
output

CASE I—EVALUATION OF DECREASED URINE OUTPUT

A 74 year old male with a history of insulin dependent diabetes, hypertension, and a "cardiac problem" suffered a perforated bowel in late January and underwent emergency surgery for repair; an ileostomy was created. He remained in the intensive care unit, but was transferred to the regular ward in early March and was begun on oral food intake. On March 15, he was begun on Neutraphos supplements when his serum phosphate was noted to be low. Pathology was consulted on March 19 because of hyperkalemia; discontinuation of Neutraphos was suggested because of high potassium content. His renal function continued to deteriorate, and Pathology was consulted again on March 25; measurement of urine electrolytes and osmolality were recommended. Urine urea nitrogen was also measured on March 25 and was 315 mg/dL. The clinical differential diagnoses were acute tubular necrosis, dehydration, or adrenal insufficiency; what is the most likely diagnosis, based on the results presented? What is the significance of the urine osmolality? What further tests would be useful?

| SPECIMEN | Na | K | Cl | CO ₂ | BUN | Creatinine | Glucose | Osmolality |
|----------|-----|------|-----|-----------------|-----|------------|---------|------------|
| Mar 15 | 135 | 4.1 | 101 | 20 | 4 | 1.1 | 251 | |
| Mar 19 | 127 | 7.4 | 97 | 22 | 31 | 1.7 | 241 | |
| Mar 25 | 122 | 7.3 | 92 | 17 | 96 | 3.4 | 208 | |
| Urine | <10 | 33.9 | <15 | | | 173.0 | | 434 |

The presence of decreased serum sodium and increased serum potassium in this case led the physicians to suspect the diagnosis of adrenal insufficiency. Because of loss of blood volume caused by sodium loss in the urine, this disease would produce a clinical picture of prerenal azotemia, with high BUN/creatinine ratio, as observed in this case. All three disorders would cause decreased urine output. Initially, based on the serum results, we suggested measurement of urine electrolytes and osmolality to further evaluate the likelihood of each disorder.

With ATN, the kidneys would not be able to conserve sodium or to concentrate the urine; both features were present in these urine chemistries. With adrenal insufficiency, dehydration is due to losses of sodium from the kidney, so that urine sodium should be increased. The low urine sodium rules out this diagnosis. This led us to conclude that prerenal azotemia was the most likely diagnosis in this case.

One problem which the clinicians had with this diagnosis was the relatively low urine osmolality. Most normal individuals should be able to produce much greater

concentration of the urine with maximal reabsorption of water under the influence of ADH. A recollection of the normal constituents of the urine will be instructive in explaining the observed results in this case. Recall that as urine passes through the tubules, most electrolyte is reabsorbed, while waste products such as urea are concentrated in the urine. When urine reaches the collecting ducts (where ADH acts), most solute is composed of urea and, to a lesser degree, sodium and creatinine. As ADH causes water reabsorption, the total solute concentration rises with urea becoming the most concentrated.

In this patient, urine urea nitrogen was only 315 mg/dL, which translates to only 112 mosm/kg. Normally, the ratio of urea to creatinine in urine averages approximately 10-15/1 (in mg/dL concentrations). In this patient, the ratio was less than 1.5/1. This low result is due to extreme malnutrition which was present in this patient. The cause for both the malnutrition and the dehydration were related to the patient's surgery. The patient had been slow to start eating again after his operation, and this caused significant loss of protein from his body. Sodium and water were being lost through the ileostomy which was created at the time of surgery.

We suggested measurement of stool volume, osmolality, and electrolyte concentration to document the amount of each being lost. Stool (ileostomy) losses were about 1.5 liter per day with a sodium concentration of 78 mmol/L. Administration of normal saline to the patient to make up for total losses plus the estimated deficit in body water resulted in normalization of all results within 5 days.

As outlined above under uses of osmometry and in the case studies, measurement of osmolality often provides information that cannot be obtained by any other method. While measurement of osmolality on a routine basis is adequate for some situations, in other patients stat measurements are essential. If screening for toxin ingestion is done in the institution, stat osmolality should be included as a rapid screen for low molecular weight toxins. Treatment of neurosurgical patients often requires calculation of osmotic gap to monitor mannitol therapy, both to assure adequate dosage and to prevent toxicity. Evaluation of patients with alteration in serum sodium or abnormal urine output is facilitated by measurement of osmolality. Because osmolality gives a more accurate measurement of urine solute concentration, it is preferred over methods based on ionic strength or specific gravity. In my laboratory, approximately 80% of our osmolalities are performed stat. Performance of osmolality within a short time of specimen collection minimizes errors which may be caused by loss of volatile substances or production of osmotically active compounds through in vitro metabolism. Because newer instruments require small volumes of specimen, are simple to operate, and provide results rapidly, I believe that osmolality should be available on a stat basis in any medical center in which the clinical problems mentioned above are seen on an emergency basis.

GENERAL REFERENCES

- Bhagat, C. I., et al.: Calculated vs measured plasma osmolalities revisited. *Clin Chem* 1984; 30:1703-1705.
- Blume, F. D., et al.: Impaired osmoregulation at high altitude. *JAMA* 1984; 252: 524-526.
- Brown, R., et al.: Renal function in critically ill postoperative patients: sequential assessment of creatinine osmolar and free water clearance. *Crit Care Med* 1980; 8:68-72.
- Davidson, D. F.: Excess osmolal gap in diabetic ketoacidosis explained. *Clin Chem* 1992; 38:755-757.
- Epstein, F. B.: Osmolality. *Emerg Med Clin North Am* 1986; 4:253-261.
- Gennari, F. J.: Current concepts. Serum osmolality. Uses and limitations. *N Engl J Med* 1984; 310:102-105.
- McLean, K. A. et al.: Influence of age on plasma osmolality: a community study. *Age Ageing* 1992; 21:56-60.
- Morton, J. J., et al.: Effect of sodium heparin on measurements of osmolality and sodium in blood. *Clin Chem* 1988; 34:1522-.
- Penney, M. D., Walters, G.: Are osmolality measurements clinically useful? *Ann Clin Biochem* 1987; 24:566-571.
- Townsend, J. C., Benton, J. M.: Serum water estimated from osmolality measurements. *Clin Chem* 1986; 32:2222-.

ELECTROLYTE DISORDERS

- Bohnen, N., et al.: Pitfalls in the measurement of plasma osmolality pertinent to research in vasopressin and water metabolism. *Clin Chem* 1992; 38:2278-2280.
- Eastep, S. J., et al.: Factitiously high sodium activities on the Ektachem 400 owing to interferences by high gamma-globulin concentrations. *Clin Chem* 1989; 35:333-334.
- Faye, S., Payne, R. B.: Rapid measurement of serum water to assess pseudohyponatremia. *Clin Chem* 1986; 32:983-986.
- Feig, P. U., McCurdy, D. K.: The hypertonic state. *N Engl J Med* 1977; 297:1444-1454.
- Geheb, M. A.: Clinical approach to the hyperosmolar patient. *Crit Care Clin* 1987; 3:797-815.
- Ladenson, J. H., Apple, F. S., Koch, D. D.: Misleading hyponatremia due to hyperlipemia: a method-dependent error. *Ann Int Med* 1981; 95:707-708.

- McKee, A. C., Winkelman, M. D., Banker, B. Q.: Central pontine myelinolysis in severely burned patients: relationship to serum hyperosmolality. *Neurology* 1988; 38:1211-1217.
- Oh, M. S., Carroll, H. J.: Disorders of sodium metabolism: hypernatremia and hyponatremia. *Crit Care Med* 1992; 20:94-103.
- Schrier, R. W.: Pathogenesis of sodium and water retention in high-output and low-output cardiac failure, nephrotic syndrome, and cirrhosis (2 parts). *N Engl J Med* 1988; 319:1065-1072, 1127-1134.
- Sterns, R. H., Riggs, J. E., Schochet, S. S.: Osmotic demyelination syndrome following correction of hyponatremia. *N Engl J Med* 1986; 314:1535-1542.
- Tryding, N., et al.: Subcutaneous and intranasal administration of 1-deamino-8-D-arginine vasopressin in the assessment of renal concentration capacity. *Nephron* 1987; 45:27-30.

TOXICOLOGY

- Baker, R. J.: Biochemical gaps: osmolal and anion. *Current Surg* 1987; 44:378-381.
- Bekeris, L., et al.: Propylene glycol as a cause of an elevated serum osmolality. *Am J Clin Pathol* 1979; 72:633-.
- Browning, R. G., Curry, S. C.: Effect of glycol ethers on plasma osmolality. *Hum Exp Toxicol* 1992; 11:488-190.
- Chan, K. - M.: Ethylene glycol, isopropanol, and methanol. *Clin Chem News* May 1989, 18-19.
- Draviam, E. J., Custer, E. M., Schoen, I.: Vapor pressure and freezing point osmolality measurements applied to a volatile screen. *Am J Clin Pathol* 1984; 82:706-.
- Eisen, T. F., Lacouture, P. G., Woolf, A.: Serum osmolality in alcohol ingestions: differences in availability among laboratories of teaching hospital, nonteaching hospital, and commercial facilities. *Am J Emerg Med* 1989; 7:256-259.
- Enger, E.: Acidosis, gaps, and poisonings. *Acta Med Scand* 1982; 212:1-3.
- Eskew, L., Speicher, C. E.: Using anion and osmolal gaps to diagnose the cause of intoxication. *Diagnostic Med*, February 1985, p. 6.
- Galvan, L. A., Watts, M. T.: Generation of an osmolality gap-ethanol nomogram from routine laboratory data. *Ann Emerg Med* 1992; 21:1343-1348.
- Geller, R. J., et al.: Serum osmolal gap and ethanol concentration: a simple and accurate formula. *Clin Toxicol* 1986; 24:77-84.
- Jacobsen, D., et al.: Anion and osmolal gaps in the diagnosis of methanol and ethylene glycol poisoning. *Acta Med Scand* 1982; 212:17-20.

- Lolin, Y., et al.: Cerebral depression due to propylene glycol in a patient with chronic epilepsy - the value of the plasma osmolal gap in diagnosis. *Postgrad Med J* 1988; 64:610-613.
- Pappas, A. A., Gadsden, R. H., Taylor, E. H.: Serum osmolality in acute intoxication: a prospective clinical study. *Am J Clin Pathol* 1985; 84:74-79.
- Snyder, H., et al.: Accuracy of blood ethanol determination using serum osmolality. *J Emerg Med* 1992; 10:129-133.
- Walker, J. A., et al.: The missing gap. A pitfall in the diagnosis of alcohol intoxication by osmometry. *Arch Intern Med* 1986; 146:1843-1844.

THERAPEUTIC DRUG MONITORING

- Dorman, H. R., Sondheimer, J. H., Cadnapaphornchai, P.: Mannitol-induced acute renal failure. *Medicine* 1990; 69:153-159.
- Rothenberg, D. M., Berns, A. S., Ivankovich, A. D.: Isotonic hyponatremia following transurethral prostate resection. *J Clin Anest* 1990; 2:48-53.
- White, R. J., Likavec, M. J.: The diagnosis and initial management of head injury. *N Engl J Med* 1992; 327:1507-15.

URINE MEASUREMENTS

- Burkhardt, A. E., et al.: A reagent strip for measuring the specific gravity of urine. *Clin Chem* 1982; 28:2068-1072.
- Dorizzi, R., et al.: Refractometry, test strip and osmometry compared as measure of relative density of urine. *Clin Chem* 1987; 33:190-.
- Dyck, R. F., et al.: A modification of the urine osmolal gap: an improved method for estimating urine ammonium. *Am J Nephrol* 1990; 10:359-362.
- Kirschbaum, B. B.: Evaluation of a colorimetric reagent strip assay for urine specific gravity. *Am J Clin Pathol* 1983; 79:722-725.
- Magner, P. O., et al.: Interpretation of the urine osmolality: the role of ethanol and the rate of excretion of osmoles. *Clin Invest Med* 1991; 14:355-358.
- Pradella, M., Dorizzi, R. M., Rigolin, F.: Relative density of urine: methods and clinical significance. *Crit Rev Clin Lab Sci* 1988; 26:195-242.

STOOL MEASUREMENTS

- Duncan, A., Robertson, C., Russell, R. I.: The fecal osmotic gap: technical aspects regarding its calculation. *J Lab Clin Med* 1992; 119:359-363.
- Eherer, A. J., Fordtran, J. S.: Fecal osmotic gap and pH in experimental diarrhea of various causes. *Gastroenterology* 1992; 103:545-551.
- Epstein, M.: Watery diarrhea and stool osmolality. *Clin Chem* 1983; 28:911-.
- Shiau, Y. - F., et al.: Stool electrolyte and osmolality measurements in the evaluation of diarrheal disorders. *Ann Int Med* 1985; 102:773-775.

EXPERIMENTAL USES

- Giacoia, G. P., Miranda, R., West, K. I.: Measured vs calculated plasma osmolality in infants with very low birth weights. *Am J Dis Child* 1992; 146:712-717.
- Hirasawa, H., et al.: Prognostic value of serum osmolality gap in patients with multiple organ failure treated with hemopurification. *Artif Organs* 1988; 12:382-387.
- Holt, A. W., et al.: Plasma osmolality changes during liver transplantation. *Transplant Proc* 1991; 23:1986-1987.
- Inaba, H., Hirasawa, H., Mizuguchi, T.: Serum osmolality gap in postoperative patients in intensive care. *Lancet* 1987; 1:1331-1335.
- Roberts, S. B., et al.: Objective verification of dietary intake by measurement of urine osmolality. *Am J Clin Nutr* 1991; 54:774-782.
- Shanfield, et al.: Synovial fluid osmolality in osteoarthritis and rheumatoid arthritis. *Clin Ortop* 1988; 235:289-295.
- Trost, H. A., Gaab, M.R.: Plasma osmolality, osmoregulation and prognosis after head injury. *Acta Neurochir* 1992; 116:33-37.
- Wilson, D. M., Anderson, R.L., Stevens, B.S.: Quantitative assessment of proteinuria from a urinary protein/osmolality ratio in a random urinalysis. *Am J Clin Pathol* 1992; 98:365.

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