The Characterization of Human Urine for Specimen Validity Determination in Workplace Drug Testing: A Review

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Abstract

One challenge facing the laboratory forensic toxicologist today is verifying the validity of the random urine specimen submitted for workplace drugs of abuse analysis. Determining whether urine substitution has occurred is best accomplished through the inspection of the specimen's appearance and the performance of specific laboratory tests, such as determining the concentration of biochemical metabolic waste products and measuring indices of urine concentration. Criteria for classifying submitted urine as substituted are postulated after an extensive review of the published scientific literature. Relevant studies that were evaluated include normal random urine reference interval studies, clinical studies involving the analysis of random urine specimens, theoretical dilutional limits, medical conditions resulting in overhydration, and water-loading studies. After compilation of the study data, derived substituted criteria of urinary creatinine ≤ 5.0 mg/dL and urinary specific gravity ≤ 1.001 are suggested. A urine specimen meeting these criteria may be considered substituted because it is not consistent with the clinical characteristics associated with normal human urine.

Introduction

Verifying the validity of random urine specimens submitted for workplace drug testing is a very difficult challenge. Because of the consequences of a confirmed-positive workplace drug test, the urine donor may attempt to conceal illegal drug use. The intent of the donor who is trying to subvert the drug testing procedure is to create a false-negative test result through specimen tampering. Tampering typically takes one of three forms—urine dilution, substitution, or adulteration. The goal of urine dilution, either in vivo or in vitro, is to produce urine whose excreted drug concentration is below that drug's screening cutoff. Manipulative polydipsia is the in vivo dilution of urine through the ingestion of a large quantity of liquid prior to urine sample collection. In vitro dilution involves the addition of liquid to a previously voided urine sample. The urine substitution process may be either natural or artificial. Natural substitution is very difficult to detect analytically because another individual's urine is submitted in place of the donor's. The substitution of urine with a liquid that resembles urine in its outward appearance, such as lemon juice, Mello Yellow®, or even water, is artificial substitution. Urine adulteration involves the addition of chemicals to the urine to mask the presence of the illicit drug, typically by interfering with drug analyses. If undetected, false-negative results due to tampering undermine the public's confidence in drug-testing programs. In this review, the characteristics of physiologically normal and abnormal random urine specimens are derived from studies and medical conditions that produce overly dilute urine. From these studies, criteria for classifying a random urine specimen as inconsistent with normal human urine are developed.

Random Urine Specimen Appearance

Urine is an aqueous solution produced by the kidneys. Its major constituents are primarily electrolytes, metabolic excretory products, and other substances eliminated through the kidneys. The initial characterization of a urine specimen is based on its appearance. Color, clarity, odor, and foaming properties contribute to the appearance of urine.

Color

The color of a urine specimen is related to the concentration of its various constituents, most notably urochromes which exhibit yellow, brown, and red pigments. A normal first morning void has a distinct deep yellow color that is more highly colored than a 0.1 g/L potassium dichromate solution (1). It should not be colorless. This characteristic yellow color is predominately caused by the presence of urobilinogen, a hemoglobin breakdown product. After hydration, urine is usually straw-colored, indicating dilute urine. Very dilute urine is essentially colorless and has a waterlike appearance (1).

About 95–99% of random urine specimens submitted to the clinical laboratory for urinalysis testing are yellow in color. The remaining 1–5% are a variety of colors, caused by either endogenous or exogenous substances derived from food pigments, medications, or disease states which produce excessive amounts of normal analytes (2).

Clarity

A normal fresh void is clear and transparent. Freshly voided urine that is cloudy or turbid can indicate the presence of white blood cells, red blood cells, epithelial cells, or bacteria. Upon standing, flaky precipitates from urinary tract mucin may appear in the specimen. Aged alkaline urine may become cloudy because of crystal precipitation. After a lipid-rich meal, the urine may also become alkaline and cloudy.

Odor

Freshly voided urine is normally odorless. With age, urine acquires a characteristic aromatic odor. As the constituents in the urine decompose, ammonia, putrefaction compounds, and hydrogen sulfide are detected. Certain foodstuffs, such as coffee, garlic, or asparagus, give urine a distinctive scent. Poorly controlled diabetic patients produce ketone bodies such as acetone, which impart a fruity odor to urine.

Foaming

The urine foaming test involves visually noting for 1 min the amount of foam remaining on the surface of a 1.0-mL urine aliquot after vigorously shaking the sample for 10 s (3). This foam is caused by the presence of protein in the specimen, and foam bubbles should not exhibit the rainbow appearance that is indicative of soap contamination.

Biochemical Properties of Urine

The kidneys filter plasma, reabsorb most of the dissolved substances that are filtered, secrete some of these substances back into its filtrate, and leave behind a concentrated solution of metabolic waste known as urine.

Normally, the plasma concentration of critical analytes is tightly controlled at the expense of urine. The kidneys help maintain these plasma critical analytes within a narrow range of normality through their filtration, reabsorption, and secretion functions. Metabolic waste products, on the other hand, are present in urine at much higher concentrations. To illustrate kidney function, a comparison of the concentrations of critical and metabolic waste analytes in serum and urine is presented in Table I.

The normal metabolic waste products found in urine are valuable in its characterization. Examples of metabolic waste products are creatinine, urea, and uric acid.

Creatinine

Creatinine is spontaneously and irreversibly formed from creatine and creatine phosphate in muscle. Creatinine, creatine's anhydride, is a metabolic waste product that is not reutilized by the body. Because there is a direct relationship between creatinine formation and muscle mass, creatinine production is considered constant from day-to-day provided that muscle mass remains unchanged. Because of this constant production, random creatinine results approximate 24-h collection reference intervals. Creatinine is freely filtered by the renal glomeruli and not significantly reabsorbed by the renal tubules, but a small amount is excreted by active renal tubular secretion. Creatinine is excreted at a relatively constant rate, relatively independent of diuresis, provided kidney function is not impaired. Creatinine production and excretion is age and sex dependent, with the underlying discriminator being muscle mass. Thus, levels are higher in males than females and decrease with advancing age. Urinary creatinine measurements are used clinically to assess renal function.

Urea

Urea, produced in the liver, is directly related to nitrogen metabolism and is the principal waste product of protein metabolism. Urea is used clinically to assess kidney function.

Though easy to automate and inexpensive to analyze, urinary urea test values offer no advantages over creatinine measure-

Table I. Critical and Metabolic Waste Analyte Concentrations in Serum and Random Urine Specimens

Analyte	Category	Serum	Random urine	Urine/ serum
Creatinine (mg/dL)	Waste	1	150	150/1
Urea (mg/dL)	Waste	20	3000	150/1
Uric acid (mg/dL)	Waste	5	80	16/1
Albumin (g/dL)	Critical	5	0.001	0.0002/1
Glucose (mg/dL)	Critical	90	5	0.055/1

Table II. Urine Analyte Reference Intervals (5)

Analyte	24 h	Random
Creatinine	600–2000 mg/d	18–200 mg/dL*
Osmolality	300–900 mOsm/kg	50–1200 mOsm/kg
pH	4.5–8.0	4.5–8.0
Specific gravity	1.016–1.026	1.002–1.030
Urea	12–20 g/d	none
Uric acid	250–750 mg/d	24 mg/dL

* Based on a calculation from 24-h creatinine and total urine volume reference intervals. The calculated random reference intervals by sex are 37–300 mg/dL (female) and 44–250 mg/dL (male).

ments in assessing the chemical characteristics of a urine specimen for drug testing. Because its production is related to dietary protein, urea excretion is not constant. There are no clinically accepted published random reference intervals for urinary urea; no studies were discovered that provided random normal ranges. The recommended condition for urinary urea storage is 4°C. This low (refrigerated) temperature is impractical for workplace drug-testing specimens that are collected and transported at ambient temperature.

Uric acid

Uric acid is a degradation product of purine metabolism. Excretion is related to gender and is highly dependent on the amount of purine in the diet. The amount excreted is roughly about 6–12% of the urate filtered by the kidney. Clinically, uric acid detection in urine is used to assess gout and the propensity to form stones.

Like urea, urine uric acid analysis offers no advantages over creatinine measurements. Urinary uric acid concentration is highly dependent on the amount of purine in the diet and thus excretion is not constant. In urine, uric acid salts, which are not readily soluble, may potentially form. In order to dissolve urinary uric acid crystals, a labor-intensive alkaline pH adjustment is required. Only one random urine reference interval study was identified; no studies that used uric acid as a test for urine characterization were found. The stability of urinary uric acid is confined to three days at room temperature. Many drugs exhibit a uricosuric effect, causing an increase in uric acid excretion.

Other Characteristics of Urine

Specific gravity

Specific gravity assesses urine concentration, or the amount of dissolved substances present in a solution. As increasing amounts of substances are added to urine, the concentration of these dissolved substances and the density, or the weight of the dissolved substances per unit volume of liquid, increases.

Specific gravity varies greatly with fluid intake and state of hydration. It is used clinically to judge the adequacy of the renal concentrating mechanism.

Osmolality

Like specific gravity, osmolality determines the concentration of dissolved substances. As the amount of dissolved substances increases, the osmolality increases.

Osmolality varies with fluid intake and level of hydration. Osmolality is used clinically to assess the diluting and concentrating capacity of the kidneys.

pH

pH is the inverse logarithmic function of hydrogen ion concentration. It serves as an indicator of the acidity of a solution. The two organs that are primarily responsible for regulating the extremely narrow blood pH range that is compatible with human life are the lungs and the kidneys. The kidneys maintain the blood pH range by eliminating metabolic waste products.

The pH of the urine is used clinically to assess the ability of the kidneys to eliminate toxic substances. Urinary pH undergoes physiological fluctuations throughout the day. Urinary pH values are decreased in the early morning followed by an increase in the late morning and early afternoon. In the bacteria-contaminated urine specimen, pH will increase upon standing because of bacterial ammonia formation.

Specimen Collection

The ideal random urine specimen is the first morning void, before the ingestion of any liquids. This sample is usually the

Table III. Random Clinical Studies

Number of subjects/samples	Creatinine range (mg/dL)	SG range	Population	Notes	Subject information	Ref.
14	≥ 10	1.002–1.024	Medical		Volunteers	6
350	172 ± 81		Medical	All creatinines > 10 mg/dL	Navy recruits	6
50	1.1–29	1.001–1.084	Drug	No paired data	Drug donors	7
176	1.1–361		Drug		Heroin abusers	8
10	183 ± 85		Medical		Healthy male staff (20–38 y)*	9
9	18–532	1.002–1.036	Drug	1206 samples	Male drug abusers	10
1601		1.000–1.055 (binned data)	Drug	0.37% in 1.000–1.005 data bin	1988 summer Olympic athletes	11
423		1.001–1.040	Drug	10% in 1.001–1.010 data bin	1988 winter Olympic athletes	12
37	20–477		Medical		14 volunteers (19 M, 4 F); 27 patients (8 M, 22 F, 27 – 67 y, 57 –266% of ideal body weight)	13
67	18–200		Medical		Turkish patients (33 M, 34 F, 16–85 y)	14
7	7–318	1.001–1.029	Drug		Drug abusers (5 M, 2 F, 25–36 y)	15
6	6–360		Drug	*n* = 955 specimens	Male drug abusers	16

*Abbreviations: M, male; F, female; y, years; m, months; B, black; W, white.

most concentrated and thus ideal for detecting low drug concentrations. This collection, of course, is impractical for a workplace drug-screening program. No preservatives are required in specimens collected for urine drug testing. Urine analytes for creatinine, osmolality, pH, and specific gravity are generally stable at least four days at room temperature.

To acquire a minimally dilute urine specimen, the donor's fluid ingestion is limited; collection should occur within 2 h of donor notification to avoid manipulative polydipsia.

The temperature of freshly voided urine is within 1.8°F (1.0°C) of the oral body temperature (4).

Overly Dilute Urine Literature Review

Criteria are needed to objectively identify those urine specimens that do not exhibit the characteristics associated with normal human urine. A review of the literature revealed no studies that specifically posed and answered the question "How can one determine with certainty whether a specimen is urine or not?" Therefore, several approaches were designed to attempt to answer this question. Literature studies that were evaluated included: (1) clinical normal random urine reference interval reports in medical texts; (2) clinical studies involving the analysis of random urine specimens; (3) theoretical limits; (4) medical conditions resulting in overly dilute urine; and (5) water-loading studies.

Random urinary reference interval studies

The first approach to the understanding of what characterizes normal human urine is to research the clinically accepted reference intervals for normal urine specimens. By clinical definition, reference intervals encompass 95% of the normal healthy population. The excluded values provide guidance regarding those results that are considered abnormal. Most urinary analyte reference intervals refer to 24-h collections that serve as a concentration average over time. Clinical data on random urine reference intervals is very limited. A summary of the clinical reference intervals is in Table II (5).

Random urine clinical studies

To validate the published clinical reference intervals, the literature was surveyed for studies enrolling normal subjects for either medical or substance abuse related conditions. Only those studies reporting creatinine and/or specific gravity in random urine specimens are summarized in Table III (6–16).

Theoretical urinary dilution limits

Clinical reference intervals assist in delineating normal from abnormal, but they do not necessarily define what is physiologically possible and what is not. By understanding the function of the kidneys, the organs that produce urine, physiological limits can be extrapolated.

The second approach proposes a clinical model that reflects the physiological diluting limits of the kidneys and thus the most physiologically dilute urine that can be produced. The renal free water excretion capacity of the kidneys is 20 mL/min which equals about 29 L/d (17–19). Under normal circumstances, the kidneys are capable of handling even the most severe water load, but ingestion of water quantities greater than about 20 L/d leads to a potentially fatal condition known as water intoxication (17,18). Death due to untreated hyponatremia and cerebral edema can occur.

Using the free water excretion capacity of the kidneys and the fluid load that produces physiological consequences, the concentrations of the various urinary constituents are theoretically abstracted to the dilutional limits of the kidney. Table IV summarizes the theoretical dilution limits for certain urinary analytes at a water excretion amount of 29 L/d. For comparison, daily excretion volumes of 20, 10, and 1 L/d, the normal excretion volume, are also included in Table IV.

Creatinine. Regardless of sex, normal adult creatinine excretion varies between 0.5 and 2.6 g/d (average 1.1–1.4 g/d) (20). Using the lowest daily creatinine excretion of 0.5 g/d and a daily urine maximum total volume of 29 L, the lowest extrapolated creatinine is 1.7 mg/dL.

Osmolality. The lowest osmolality possible in the renal collecting duct is 50 mOsm/kg (21). The range for random urinary

Table IV. Theoretical Dilution Limits of Urinary Analytes

Analyte	29 L Theoretical limit	20 L Theoretical limit	10 L Theoretical limit	1 L Theoretical limit
Creatinine (mg/dL)	1.7	2.5	5.0	50
Osmolality (mOsm/kg)	7	10	20	200
Specific gravity	1.001	1.001	1.002	1.019

Table V. Medical Conditions that Result in Polyuria

Condition	Description*
Psychogenic polydipsia	Excessive fluid consumption resulting from a disorder in personality, without a demonstrable organic lesion. Various psychological disorders, such as schizophrenia, and head trauma and drug side effects typically contribute to the development of this condition.
Water intoxication	Severe overhydration which may result in convulsions and death due to uncorrected hyponatremia and cerebral edema
Diabetes insipidus	The chronic excretion of very large amounts of pale urine of low specific gravity, accompanied by extreme thirst, resulting from inadequate amounts of pituitary antidiuretic hormone (ADH)
Nephrogenic diabetes	The chronic excretion of very large amounts of pale urine of low specific gravity resulting from the inability of the kidneys to respond to ADH
Iatrogenic diabetes	Diabetes introduced by an unfavorable response to a therapeutic intervention

* Definitions were abstracted from the *Illustrated Stedman's Medical Dictionary*, 24th ed. Williams & Wilkins, Baltimore, MD, 1982.

Table VI. Medical Polyuria Case Studies

Number of subjects	Condition	Creatinine (mg/dL)	SG	Osmolality (mOsm/kg)	Notes	Subject information	Ref.
11	Psychogenic polydipsia		1.002–1.024	45–530		10 M, 1 F, 42–67 y, 6 B, 5 W	22
1	Diabetes insipidis		1.003	106	12–15 L/d	24 y Mexican-American M	23
1	Diabetes insipidis		1.007	296	8.5 L/d	24 y Mexican-American M	23
1	Psychogenic polydipsia			84	> 6 L in "few" h	34 y F	24
1	Water intoxication			237	6 L/d	26 y F, 43 lb	25
1	Water intoxication			142	19 L/6 h	18 y Eskimo Army recruit M	26
1	Water intoxication			78	1.44 L, seizures, coma	F child	27
1	Diabetes insipidis	13	1.005	54	4–6 L/d	53 y F	28
10	Psychogenic polydipsia	4–185	1.000–1.017		No paired data	8 M, 2 F (28–53 y, 136–189 lb)	29
35	Polydipsia			144 ± 23		Study population (15 M, 20 F, 61–87 y)	30
1	Iatrogenic polydipsia			313	15–18 L/d	56 y M	30
14	Polydipsia			122 ± 66		13 M, 1 F (21–55 y)	31
			112 ± 57				
10	Polydipsia			> 50	20 mL/kg water load in 10 min	21–55 y	32
1	Psychogenic polydipsia			154		46 y M	33
1	Psychogenic polydipsia			141		43 y W	34
1	Water intoxication		1.000	80		64 y F W	35
1	Water intoxication			55		26 y M	36
1	Water intoxication			87		10 m F (21 lb)	37
1	Water intoxication			203	Ingested 3 L/3 h	40 y F (121 lb)	38
1	Water Intoxication		1.000		Ingested 24 L/10 h	45 y M ultramarathoner (180 lb, 6'3")	39
4	Psychogenic polydipsia			143–342		56 y F, 52 y M, 73 y F, 67 y F	40
2	Water intoxication		1.001–1.006			4 m M B (13 lb 8 oz), 14 m M B	41
8	Psychogenic polydipsia		1.001–1.010	56–176	Void 5–19 L/d	5 M, 3 F Japanese (31–50 y)	42
1	Water intoxication			50–60	Void 11–17 L/d	26 y M Japanese	43
11	Diabetes insipidus			100–200		7 M, 3 F (22–68 y)	44
10	Psychogenic polydipsia			225–325		7 M, 3 F (28–60 y)	44
20	Diabetes insipidus			83–303	Void 5–12 L/d	6 M, 14 F (ages 16–55)	45
4	Nephrogenic diabetes			64–190		3 M, 1 F (ages 6–33 m)	46
1	Psychogenic polydipsia			49	16 L/d	43 y F	47
1	Psychogenic polydipsia		1.001	52, 77		34 y M	48
1	Psychogenic polydipsia			197		51 y W F	49
1	Psychogenic polydipsia		1.004; 1.001–1.002	105; 32	pH 5.0	42 y F	18
1	Psychogenic polydipsia			58		41 y M	50
1	Psychogenic polydipsia		1.002			35 y M	51
1	Psychogenic polydipsia		1.001–1.004			26 y M	52
1	Psychogenic polydipsia			113		47 y F	53
1	Nephrogenic diabetes			168	> 6 L/d	36 y F	54
1	Nephrogenic diabetes		1.005–1.006, 1.002	130–140		8 y M	55
1	Diabetes insipidus/ Psychogenic polydipsia			392, 66	6 L/d	42 y F	56
1	Psychogenic polydipsia			317, 421	15 L/d	41 y M	57
1	Psychogenic polydipsia		1.004, 1.001, 1.002			15 y F	58
1	Psychogenic polydipsia		1.002	56	20–30 L/d	50 y M	59
1	Psychogenic polydipsia			38	4–8 L/d	17 y F	60
4	Psychogenic polydipsia		1.006, 1.000	154; 201; 109		46, 36, 44, 43 y M	33
1	Psychogenic polydipsia			63–80	10 L/d	42 y M	61
1	Psychogenic polydipsia		1.005		pH 6.0	38 y M	62
10	Psychogenic polydipsia		1.001–1.005	58–153			63
10	Psychogenic polydipsia		1.001–1.005		4–10 L/d		64
20	Psychogenic polydipsia		1.000–1.004	37–95	7–43 L/d		65
4	All polyuria causes		1.003–1.004	36, 112		16 y M, 7 m M, 12 y M, 22 y M	66
1	Psychogenic polydipsia		1.001			20 m M	67
2	Psychogenic polydipsia		1.000, 1.001, 1.008	23, 18, 40	pH 6.0, death	29 y F	68
2	Psychogenic polydipsia		1.005, 1.008	115		52, 54 y M	69
4	Psychogenic polydipsia		1.000, 1.003, 1.004	392	Urea 3–5 mg/dL	28, 34, 40, 44 y F	70
2	Psychogenic polydipsia		1.001, 1.002			52, 52 y M	71

osmolalities is 200–1700 mOsm/kg. A maximum daily excretion of 29 L translates into a urinary osmolality of 7 mOsm/kg, the lowest theoretical osmolality.

pH. The physiological limits for urine pH are 4.5 and 8.0. Values between 4.5 and 4.8 are found in extreme ketosis or severe infection of the kidney or bladder. In the alkaline spectrum, though a pH of 8.0 is the physiological upper limit for the kidneys, a specimen contaminated with bacteria may yield a higher pH value because of bacterial ammonia production.

Specific gravity. A specific gravity of 1.000 is considered physiologically impossible unless a large volume of water is ingested and excreted. Specific gravities > 1.040 are also physiologically impossible unless radio-opaque dye is being excreted. Normally, 50–70 g/d total solids are excreted in the urine. This 50 g/d excreted into 29 L of water would produce 172 mg/dL total solids. Using Long's equation [(the last two digits of the urine specific gravity) × 2.6 (Long's constant) = g total solids/L)], the calculated specific gravity associated with 172 mg/dL is 1.00066 (≈ 1.001), whereas that associated with 250 mg/dL is 1.00096 (≈ 1.001).

Medical overhydration studies

For comparison to the extrapolated renal theoretical limits, clinical conditions that produce overhydration or polyuria, the production of excessive amounts of urine, were identified. Because the concentration of urinary analytes is related to the urine volume, polyuria produces dilute urine. These extreme conditions that produce exceedingly dilute urine are described in Table V.

A summary of the medical case studies reporting excessive urine production and providing random urine data for creatinine, specific gravity, and/or osmolality are found in Table VI (18,22–71).

Water-loading studies

The final approach to answering the question of what is the physiologically most dilute random urine possible was to research water loading studies in which excessive amounts of water were ingested in an attempt to dilute the urine. Water-loading studies that reported random urine creatinine, specific gravity, and/or osmolality data are summarized in Table VII (6,8,15,72–78).

Discussion

One question facing the forensic toxicologist is whether the submitted workplace urine specimen is consistent with normal human urine. This review attempted to determine which urine markers at what cutoff concentrations indicate that the submitted specimen is either consistent or inconsistent with urine.

Table VII. Water-Loading Studies

Number of subjects	Dose	Creatinine range (mg/dL)	SG range	Pairs	Notes	Subject information	Ref.
6	4 mL/kg over 10 h		1.012 ± 0.002	No creatinine data	Osmolality 295 ± 69 mOsm/kg	Normal males (19–33 y, 152–185 lb)	72
1	1.2 L/1 h 1.1 L/30 min 1.4 L/75 min	32–157	1.004–1.014	Lowest pair: 32 creatinine 1.005 SG	Lowest creatinine 32 mg/dL	Volunteer	73
6	1.0–2.0 L /4 h	≥ 30	1.003–1.010			Volunteers	6
7	3.8–4.2 L/4 h	4–266	1.000–1.030	Lowest pairs: (4 : 1.003) (5 : 1.003)	SG ≤ 1.001 paired with 8–12 mg/dL creatinines	5 M, 2 F drug abusers (25–36 y, 133–316 lb)	15
2	3.4–3.8 L/4 h		1.000	No creatinine data	Only value claimed	Male staff	74
23	0.5 L/15 min	8–257			Osmolality 69–1075 mOsm/kg	Staff	8
23	1.0 L/15 min	7–257			Osmolality 45–996 mOsm/kg	Staff	8
20	0.8, 1.0 and 1.5 L/BSA (m^2)/d		1.025 (0.003) (0.8 L/BSA) 1.022(0.005) (1.0 L/BSA) 1.015(1.010) (1.2 L/BSA)			10 M, 10 F soldiers	75
8	20 mL/kg				Osmolality 32–95 mOsm/kg	Sickle cell patients	76
9	5.6 ± 1.8 L/21 h		1.005–1.025		Osmolality 200–850 mOsm/kg	Males	77
8	2.6 L fluids/2 h postexercise				Osmolality range 1 h postingestion 120–350 mOsm/kg	8 M cyclists (21–23 y, 150–158 lb)	78

Specimen appearance, including its color, clarity, odor, and foaming characteristics, is a valuable tool to assess tampering concerns. Visual inspection of the specimen, though somewhat subjective, resulted, in one study, in correct classification of 96.5% of urines previously determined to be "suspicious" (1). The Substance Abuse and Mental Health Services Administration (SAMHSA) of the U.S. Department of Health and Human Services (HHS) has addressed urine specimen appearance through issued guidance. At the time of collection it is recommended that the urine be inspected for unusual color, odor, or other signs of adulteration (79).

On the objective level, the laboratorian has many analytical tools available to evaluate the validity of the submitted urine specimen. The first of these is the temperature of the specimen at the time of collection. SAMHSA has again provided detailed standardized collection procedures with the goal of discouraging specimen tampering. Within 4 min of submission, the temperature of the urine specimen is documented. An acceptable specimen temperature range is 90–100°F (32–38°C) (79).

Because the kidneys are limited to producing urine within the pH range of 4.5 to 8.0 (note: bacterial contamination may produce urinary pH values > 8.0), pH values beyond this range are highly suspect for tampering. The pH of a solution is commonly determined with a pH electrode or an indicator dye. The pH electrode is based on the principle of potentiometry. pH paper or the automated pH methods rely on the ability of a solution's hydrogen ion concentration to cause a color change in an indicator dye. Because no indicator dye will cover the entire urinary pH normal range, most reagent strips utilize two indicators, methyl red and bromthymol blue, to provide a reportable range of 5.0 to 8.0. Indicators are usually not very sensitive, providing results with ± 0.5–1.0 pH unit accuracy. Ionic strength methods are adequate as an initial screening method, but pH values outside these limits should be verified with a pH electrode. Though pH is not useful in determining the dilutional status of urine, it is a valuable test for assessing chemical adulteration. SAMHSA in its Program Document #35 has recommended that a urine specimen be labeled adulterated if its pH is ≤ 3 or ≥ 11 (80).

The best initial biochemical screening test to evaluate the submitted specimen is urinary creatinine, a metabolic waste product. It is the test of choice because it is easy to automate, inexpensive to perform, and a well-characterized robust assay. The most common methods for the quantitation of creatinine in urine involve either the colorimetric Jaffé reaction that uses an alkaline picrate solution or an enzymatic determination. Many clinical urinary creatinine methods use a serum-optimized assay, usually the Jaffé method, and a 10- to 20-fold dilution of the urine to place urine results within the serum linearity range. Analysis of very dilute urine specimens requires omission of the clinical predilution step and inclusion of urine control materials at the SAMHSA-defined dilute and substituted decision levels. Urinary creatinine methods have adequate sensitivity (0.1 mg/dL) to detect very dilute urinary concentrations.

Although creatinine is a sensitive marker to the amount of fluid ingestion, the relationship between urinary creatinine and fluid ingestion is neither linear nor immediate. With a large intake of fluid, there is a 2:1 disparity between the intake and void volumes because the kidneys are not capable of processing large quantities of fluid within a short time after ingestion. With normal fluid intake, the void volume approximates ingestion. After fluid ingestion, 2–5 h are required to see a change in urinary creatinine (6). The ingestion of a diuretic substance, such as caffeine or alcohol, may actually shorten the time required by the kidneys to produce a dilute urine. To minimize the production of overly dilute urine, the amount of fluid that the donor ingests postnotification should be limited. Also, specimen collection should proceed as soon as possible after notification. Per SAMHSA regulations, within a 2-h period fluid ingestion is limited to 8 ounces every 30 min up to a maximum of 24 oz (79). The U.S. Department of Transportation (DOT) regulations (49 CFR Part 40) allow ingestion of up to 40 oz of fluid in 3 h.

The confirmatory test for overly dilute urine should be a measure of urine concentration, either specific gravity or osmolality.

Specific gravity, performed with a urinometer or a refractometer, measures the density of urine relative to pure water. Alternatively, specific gravity determined using a dipstick or its automated counterpart is based on the ionic strength, a substitute for specific gravity; ionic strength causes a pK_a change in certain pretreated polyelectrolytes that results in a change in the indicator color. These ionic strength tests are adversely affected by highly buffered acidic or alkaline urines, urines with pH values either < 5.0 or > 8.0 or the presence of certain elevated urinary constituents, such as protein. Ionic strength methods lack precision (typically ± 0.005) and thus low values should be verified with a refractometer.

The most common measurement method for urinary osmolality is freezing point depression. Urine osmolality is performed identically to serum with no modifications required. Freezing point depression has adequate sensitivity, with a lowest detectable concentration of about 3 mOsm/kg.

In most cases, there is a constant relationship between specific gravity and osmolality unless highly osmolar substances are present in the urine, such as radio-opaque compounds or high levels of glucose or protein. The effect of dilution on urine osmolality is dependent upon the type of fluid used for dilution. The addition of either water or osmolar substance, for instance, to a urine specimen will cause urine dilution; water addition decreases the osmolality of the urine specimen, whereas the addition of an osmolar substance leaves the osmolality relatively unchanged.

To achieve better distinction, osmolality may replace the specific gravity measurement. The theoretical lower urinary osmolality limit is 7 mOsm/kg and the lower limit of the normal random reference interval is 50 mOsm/kg, the lowest osmolality possible in the renal collecting duct. In psychogenic polydipsia, case study urinary osmolalities ranged from 18 to 450 mOsm/kg. Osmolalities < 32 mOsm/kg have proven fatal, even with intervention (68). An osmolality cutoff of 32 mOsm/kg distinguishes a physiologically dilute urine from a urine specimen that is inconsistent with urine. Though values lower than this cutoff have been observed, the clinical presentation of the patient with such a low urinary osmolality is coma or death.

The drawback to osmolality is that the procedure requires special instrumentation. Thus, specific gravity is analytically easier for laboratories to implement.

For both analytical and biochemical reasons, creatinine and specific gravity are the tests of choice to characterize urine. From a financial aspect, a two-tier approach is the most feasible. Because creatinine is a readily automated, inexpensive and robust assay, it is the logical choice for the initial test. Only those specimens falling below the cutoff would be subjected to specific gravity testing. Also this dual requirement to characterize a urine specimen as inconsistent with human urine provides both an analytical and physiological safeguard.

An extensive literature search was undertaken to establish cutoff concentrations to determine at what point the submitted sample is inconsistent with human urine. Case studies involving medical conditions that produce overly dilute urine were researched to determine the characteristics of the most physiologically possible dilute urine. These characteristics were compared to the theoretical lower limit and the lower limit of the normal reference interval to determine where the cutoff concentration exists.

For urinary creatinine, the theoretical limit is 1.7 mg/dL, whereas the lower limit of the normal random reference interval is 18 mg/dL. The lowest random urinary creatinine results found in the literature studies were 1 and 4 mg/dL. The 1 mg/dL creatinine results are suspect because they are considered theoretically impossible. Also, the 1 mg/dL results, as well as two of the 4 mg/dL results, were obtained from studies involving drug abusers as subjects. This subject population would perceive an incentive to tamper with their specimens to avoid detection, and thus the validity of their specimens is suspect. There is one medical case with a result of 4 mg/dL. This study was from 1985, and the accuracy of this result with dated technology is unknown. Based on these data, a cutoff of 5 mg/dL is proposed.

Those specimens with urinary creatinine concentrations ≤ 5 mg/dL would be subjected to specific gravity analysis, a measure of urine concentration. The theoretical limit for specific gravity is 1.001 and the lower limit of the normal random reference interval is 1.002. Inspection of the random clinical studies found three cases of specific gravity results of 1.001. Two of these cases were from drug abuse subjects, and the third was from an Olympic athlete. In the medical polyuria cases, there were seven studies having specific gravities of 1.000. An additional 11 studies had specific gravities of 1.001. With water loading, in two instances a specific gravity of 1.000 was achieved. Unfortunately, after an extensive review of the literature, very few studies were found that had paired creatinine and specific gravity data. In all of these cases, in only one instance was paired creatinine/specific gravity data available. In these data, the pairs were 4 mg/dL creatinine and 1.003 specific gravity and 5 mg/dL creatinine and 1.003 specific gravity. Thus, a cutoff of 1.001 is proposed.

For a specimen to be considered inconsistent with human urine, both creatinine and specific gravity must meet defined criteria; that is, urine creatinine ≤ 5 mg/dL and urinary specific gravity ≤ 1.001. These cutoff concentrations for creatinine and specific gravity are below the clinically accepted reference intervals for these analytes. In the random clinical and water loading studies, a few results from the substance abuse population studies had creatinine or specific gravity measurements that met or exceeded either the creatinine or specific gravity cutoffs. No paired data were available to determine whether both the creatinine and specific gravity substituted criteria were met. In the medical populations studied for random clinical and water-loading studies, no specimen was identified in which the urinary creatinine concentration was ≤ 5 mg/dL and the urinary specific gravity was ≤ 1.001. Creatinine or specific gravity values were individually low in a few cases. For those medical case studies where paired creatinine and specific gravity data did exist, no specimen was identified in which the urinary creatinine concentration was ≤ 5 mg/dL and the urinary specific gravity was ≤ 1.001.

In summary, the review of the scientific literature including random clinical studies, medical conditions resulting in severe overhydration or polyuria, and water-loading studies concludes that the criteria of creatinine ≤ 5.0 mg/dL and specific gravity ≤ 1.001 represent a specimen condition that is not consistent with normal human urine. In the deductive evaluation of 75 studies, no exception to the criteria defining a specimen inconsistent with human urine was reported.

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