Urine Screening with the UF-Series Analysers: The Use of Urine Conductivity as a Surrogate Marker of Urine Osmolality and Renal Diuresis

Eva GAZINSKY and Fritz BOEGE

Institute of Clinical Chemistry and Laboratory Diagnostics, Heinrich Heine-University, Medical School, Moorenstraße 5, D-40225 Düsseldorf, Germany.

The kidney is capable of altering the water content of the urine. Consequently, analytes in the urine are diluted in a varying volume, which poses a problem when they are to be expressed in quantitative terms. To what extent a urine specimen is subjected to diuresis/antidiuresis, can best be determined by its osmolality. However, direct osmolality measurements are not suitable for routine clinical screening, which usually employs surrogate parameters, e.g. relative density or creatinine concentration of the urine. These markers are not practical, when urine screening is performed with a Sysmex UF-Series analyser as the sole device. However, such analysers measure the electrical conductivity of each urine specimen for internal reference purposes and we propose here that conductivity can serve as a robust marker of diuresis/antidiuresis. It correlates precisely with the urinary concentration of sodium and potassium, whereas it is insensitive to urea and glucose. Thus, conductivity faithfully monitors urinary electrolyte concentration, but is not influenced by pathological conditions altering urine osmolality in a fashion unrelated to diuresis. It should also be noted that conductivity correlates well with urinary creatinine concentration, a surrogate parameter of diuresis used for reference purposes. In summary, conductivity is a superior surrogate parameter for judging the state of diuresis in routine urine screening and is a suitable reference value for quantitative determinations of other urine analytes. When it comes to judging the osmotic labour of the kidney in the presence of increased concentrations of non-ionic osmolytes such as glucose or urea, conductivity complements measurements of osmolality.

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INTRODUCTION

The determination of urinary water content is of clinical interest in several ways. On one hand, the capability of concentrating or diluting the urine is one of the most complex functions of the kidney and loss of this function is one of the most sensitive indicators of renal failure. On the other hand, all urinary analytes are dissolved in a varying volume of urine and their interpretation in quantitative terms requires the state of diuresis to be known. Finally, the water content of the urine is of much interest, when the state of hydration of a patient is to be controlled and balanced.

The water content of a urine specimen has to be assessed in an indirect manner, as it is reflected by the cumulative concentration of all the substances dissolved in it. Since there is no way of measuring the entire solute complement, single analytes or groups of substances have to be taken *pars pro toto*. Typical surrogate parameters are osmolality, relative density (specific weight), creatinine concentration, and conductivity[1]. Urine osmolality is considered the gold standard for determining the osmotic labour of the kidney and for controlling hydration of a patient[2]. In most settings of routine clinical screening it has been replaced by the less cumbersome determination of relative density[3-5], or by semiquantitative colorimetric reactions reflecting the relative density that are even more practical[6-8]. Urine creatinine concentration, on the other hand, is the parameter most often used as an internal standard for the quantitative expression of urinary analytes such as proteins[9]. Electric conductivity, finally, is the gold standard for determining the salt content of aqueous samples in environmental toxicology[10] and could, in theory, be put to a similar use in medical urine analysis[1, 11].

In the setting of a conventional diagnostic laboratory changing from urine density determination by an integrated dip-stick test to urine conductivity by a separate electrical measuring device would not hold obvious advantages. However, a different situation arises, when a urine flow cytometer - such as the fully automated urine cell analyser, UF-100 (Sysmex Corporation, Kobe, Japan) - is used as the sole device for urine screening analysis[12], because this analyser measures *inter alia* electric conductivity of the urine for internal reference purposes. Thus, in this situation the use of conductivity instead of other surrogate parameters of urine "concentratedness" would be clearly advantageous with respect to cost effectiveness and work-flow economics. In this report we address the question of how the major carriers of urine osmolality are represented by conductivity and how urine conductivity differs in terms of clinical interpretation from other surrogate parameters describing the state of diuresis.

MATERIALS AND METHODS

Electric conductivity was measured with a urine flow cytometer Model UF-100 or with a temperature controlled microprocessor conductivity meter Model LF96 equipped with a 4-electrode sensor Model TetraCon 96 (both Wissenschaftlich-Technische-Werkstätten GmbH, Weilheim, Germany). Osmolality was measured with a kryo-osmometer Model 38671 (Knauer, Berlin, Germany). Dipstick analysis of urinary salt content was done with the Combur 10 Test M (Roche Diagnostik, Mannheim, Germany) using the Miditron M device (Boehringer, Mannheim, Germany) for colorimetric quantification of the results. Relative density was measured by volume displacement using a calibrated spindle device. Concentrations of sodium and potassium were measured by atomic absorption using an AFM 5051 (Eppendorf Gerätebau, Netheler und Hinz GmbH, Hamburg, Germany). Concentrations of glucose, creatinine, and urea were determined by standard procedures using a Hitachi 717 automatic analyser (Boehringer, Mannheim, Germany) and reagents from the same manufacturer. Aqueous solutions containing defined concentrations of NaCl, KCl, and urea were prepared from double distilled water and chemicals of the highest degree of purity commercially available.

RESULTS

The water content of an aqueous solution is reflected by the concentration of the major osmolytes, encompassing, in the case of human urine, NaCl, KCl, urea, and possibly glucose. First, we investigated, how these four major osmolytes of human urine are represented by measurements of osmolality, relative density, and conductivity. For this purpose we prepared aqueous solutions containing the above osmolytes at defined concentrations and compared by regression analysis the true concentrations with corresponding measurements of osmolality, relative density, and conductivity. Measurements of osmolality and conductivity were compared to molar concentration, whereas measurements of relative density were compared to mass concentration (mg/L), with the mass concentration of water (i.e. 1000) added in order to obtain values comparable to relative density expressed as ‰. The results are summarized in ***Table 1***. It can be seen that osmolality measurements correlated with the concentrations of ionic and polar osmolytes in a similar fashion. The slopes of the regression lines were, in all cases, close to 1.0, indicating that the molar concentrations of all major osmolytes of human urine are reflected in a congruent manner by osmolality measurements. A similar but slightly less controlled situation was encountered with relative density measurements, where reasonable linear correlations were obtained for all four osmolytes. However, the slopes of the regression lines were in all cases significantly smaller than 1.0 and dissimilar between ionic and polar osmolytes, suggesting that measurements of relative density underestimate the concentrations of osmolytes to a varying degree. Ionic substances are underestimated by about 30%, whereas polar osmolytes are underestimated by 60-70%. It should, moreover, be noted, that these findings apply only to measurements with a displacement spindle, whereas measurements of ion content with a routine dipstick reagent showed no correlation at all with the concentration of any of the four osmolytes studied here (not shown) and it was not possible for us to determine, which urinary analytes are actually reflected by such assays. As may be deduced from the data at the bottom of ***Table 1***, we found an excellent correlation of conductivity both with NaCl and KCl, although the latter seems to be overrepresented due to its higher electric activity (compare slopes). No correlation was observed between conductivity and the concentration of urea or glucose and it should be noted that

Table 1 *Correlation with defined concentrations in synthetic aqueous solution*

	NaCl	KCl	Urea	Glucose
Osmolality				
Regression	linear	linear	linear	linear
Slope (mol·osmol^{-1})	0.92	0.96	0.97	0.96
R	0.999	0.999	0.999	0.980
Relative Density				
Regression	linear	linear	linear	linear
Slope (dimensionless)	0.72	0.71	0.28	0.37
R	0.981	0.993	0.931	0.999
Conductivity				
Regression	linear	linear		
Slope (S·L·cm^{-1}·mol^{-1})	0.078	0.125		
R	0.998	0.999		

these substances did not increase conductivity at all when present at concentrations similar to those found in human urine. Thus, conductivity differs markedly from osmolality and relative density in as much as it is exclusively sensitive to electrolytes and does not at all encompass polar osmolytes.

Next we tried to determine if these findings obtained in synthetic solutions would also hold true in the much more complex setting of actual human urine samples. To test this, we derived, from the data shown in ***Table 1***, a set of formulae allowing a prediction of conductivity, osmolality, or relative density on the basis of measured concentrations of NaCl, KCl, glucose, and urea.

The formulae were as follows (squared brackets indicating millimolar concentrations):

Osmolality (mosmol·l^{-1}) = [Na]·0.92 + [K]·0.93 + [Cl]·1.8 + [glucose]·1.12 + [urea]·0.973

Density (‰) = [Na]·0.361 + [K]·0.355 + [Cl]·0.716 + [glucose]·0.369 + [urea]·0.238

Conductivity (mS·cm^{-1}) = [Na]·0.0388 + [K]·0.0626 + [Cl]·0.1014

We then collected 50 samples of spot urine, measured Na, K, Cl, glucose, and urea and calculated, thereof, the predicted values for osmolality, relative density, and conductivity. These were compared by linear regression with corresponding values obtained by direct measurements. It should be noted that conductivity was in this case measured with the UF-100. These comparisons are plotted in ***Fig. 1*** and the results of regression analysis are summarized in ***Table 2***.

It can be seen that an excellent correlation between predicted and measured values was obtained for osmolality (***Fig. 1A***) and conductivity (***Fig. 1C***), whereas a much lesser correlation was obtained for relative density (***Fig. 1B***) due to the inherent imprecision of the method. It should be mentioned that in the case of conductivity the slope of the regression line was only 0.75, which is most probably due to a different temperature compensation of the conductivity meter of the UF-100. In summary, these data indicate that our findings obtained with synthetic solutions can be applied to urine samples and that conductivity and osmolality may also be regarded as complementary parameters in as much as the one encompasses all osmolytes, whereas the other is selective for electrolytes.

Having thus established the utility of conductivity as a suitable surrogate marker of urinary electrolyte concentration, we asked ourselves if it could be also used as a reference value for quantitative determinations of other urinary analytes in the same fashion as urine creatinine. To test this we compared the concentration of creatinine in 45 specimen of spot urine with measurements of osmolality, relative density (displacement spindle), and conductivity (measured with the UF-100). These comparisons are plotted in ***Fig. 2*** and the results of linear regression analysis are summarized in ***Table 3***.

It can be seen that conductivity and osmolality showed a similar degree of correlation with urine creatinine concentration, which showed less scatter (***Fig. 2***, compare ***B*** to ***C***) and was clearly better (R=0.839 vs. R=0.7828) than that of relative density. An interpretation of the slope values is not meaningful in this case. Thus, conductivity

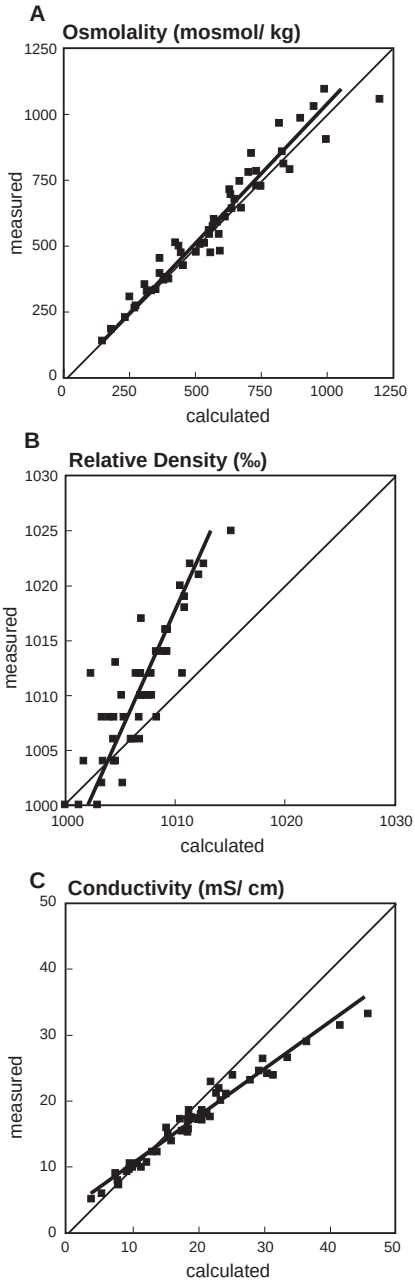

Fig. 1 *Comparision of measured values of urinary osmolality (A), relative density (B), and conductivity (C) with corresponding values predicted from measurements of Na, K, C1, urea, and glucose. Thick line shows result of linear regression, Identity is represented by thin line.*

Table 2 *Correlation of expected vs. measured values in spot urine*

	Slope (measured·calculated^{-1})	R
Osmolality	1.037	0.972
Relative density	1.716	0.878
Conductivity	0.752	0.982

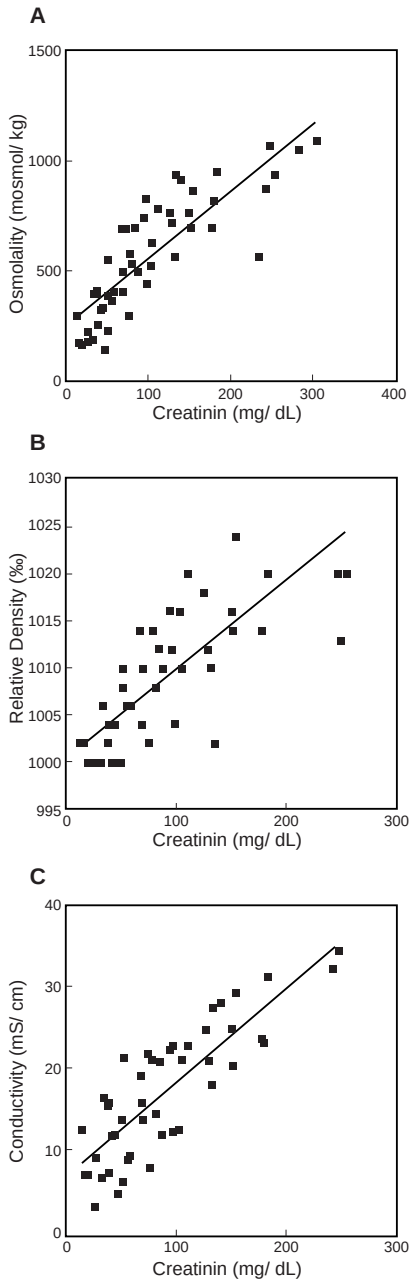

Fig. 2 *Comparison of urine creatinine concentration with measured values of osmolality (A), relative density (B), and conductivity (C). Thick line shows result of linear regression.*

Table 3 *Comparison with creatinine concentration in spot urine*

	Slope	R
Osmolality	3.498	0.853
Relative density	0.089	0.7828
Conductivity	0.108	0.839

can be used in the same way as urine creatinine concentration as a reference value for expressing other urinary analytes in quantitative terms. Moreover, the analytical performance of conductivity in this respect is as good as that of osmolality and clearly better than that of relative density.

DISCUSSION

In summary, our data show that urine conductivity can be used as surrogate parameter of diuresis in a similar fashion to relative density and creatinine concentration. When used in conjunction with osmolality measurements, conductivity allows a differentiation of water diuresis and osmotic diuresis (due to an increased excretion of non-ionic osmolytes), which is not possible on the basis of osmometric data alone[13]. Taking into consideration that conductivity can be measured at no additional expense, providing the UF-100 is being used for sediment analysis, it should be considered as a parameter clearly superior to the determination of urinary salt content by dipstick methods. The use of conductivity for gauging the cumulative concentration of all substances dissolved in urine is clearly attractive in situations, where a urine flow cytometer is used as the sole device for urine screening, because it eliminates the need to determine relative density manually with a displacement spindle.

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