CLIN. CHEM. 29/8, 1508–1512 (1983)

Potentiometry of Na^+ in Undiluted Serum and Urine with Use of an Improved Neutral Carrier-Based Solvent Polymeric Membrane Electrode

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We present an improved Na^+-selective liquid membrane electrode for measurement of Na^+ concentrations in both undiluted serum and urine. The values for urinary Na^+ obtained with the ion-selective electrode agree well with those obtained with the flame photometer. The correlation gives a standard residual deviation of ± 2.7 mmol/L over the Na^+ range of 25–280 mmol/L. In serum, this direct potentiometry yields Na^+ concentrations 5.4% (SD 1.1%) higher than those obtained by atomic spectrometry and a standard residual deviation of ± 1.1 mmol/L. Correction of these values for the volumes of protein and lipid leads to potentiometric values 1.2% (SD 0.7%) lower than those by flame photometry (residual standard deviation: ± 1.0 mmol/L). Other factors that possibly contribute to this discrepancy are discussed.

Additional Keyphrases: *ion-selective electrodes · potentiometry, flame photometry, and atomic absorption spectrometry compared*

Glass-membrane electrodes are routinely used for determination of Na^+ in whole blood (*1, 2*), plasma (*1, 3–5*), serum (*1, 5–8*), and diluted urine (*1, 5, 8–11*). Their widespread use does not necessarily imply the absence of drawbacks, however. Devising a leak-proof joint between the glass-membrane electrode body and the channel of miniaturized flow-through systems (clinical analyzers) poses technical problems. Other difficulties arise from the contamination of the glass-membrane surface—e.g., by proteins—and the rather high specific resistance of glass membranes. Liquid membranes are to be preferred in this connection.

There are various ways of mounting membranes in electrode half-cells: casting, clamping, or glueing. Several half-cells and a reference cell can be differently configured to obtain a miniaturized flow-through electrode system (*12*). Because membranes in such systems remain functional even after extended contact (several months) with whole blood and blood serum (*13*), they do not need special treatment at regular intervals to regenerate the membrane surface (*9*), e.g., to remove protein depositions. The specific resistance of typical solvent polymeric membranes can be several orders of magnitude lower than for glass electrodes (see reference *14* and Table 1).

Here we present a new Na^+-selective liquid membrane that can be used for direct measurements in blood and urine. An important advantage of this direct potentiometry is that one can determine the physiologically more relevant ion-activities in plasma water (*15, 16*). These values are not influenced by proteins and lipids (*4, 16–20*), whereas indirect atomic spectroscopic measurements can lead to dangerous errors in plasma concentrations of Na^+ in cases of hyperproteinemia or hyperlipidemia (*21–23*). Pseudohyponatremic Na^+ values lower than 120 mmol/L have been reported, when the sodium concentration after lipid extraction on the same samples exceeded 200 mmol/L (*23*).

Materials and Methods

Reagents and Samples

The aqueous electrolyte solutions were prepared in water doubly distilled in quartz, and the salts were of the highest purity available. Ligand 1 (*N,N'*-dibenzyl-*N,N'*-diphenyl-1,2-phenylenedioxydiacetamide) was prepared according to Vögtle et al. (*24*) and corresponds to the Na^+-ionophore II (ETH 157, cat. no. 71733; Fluka AG, CH-9470 Buchs, Switzerland). The synthesis of ligand 2 (1,1,1-tris[1'-(2'-oxa-4'-oxo-5'-aza-5'-methyl)dodecanyl]propan) is described in detail by Güggi et al. (*25*) and corresponds to Na^+-ionophore I (ETH 227, Fluka no. 71732). Bis(1-butylpentyl)adipate (purum p.a. grade; BBPA) was synthesized as described in reference *26* (it also is available from Fluka AG, as no. 02150) and the high-molecular-mass poly(vinylchloride), PVC S 704, was obtained from Lonza AG, CH-3930 Visp, Switzerland, but can now also be obtained from Fluka AG (no. 81392). Tetrahydrofuran (puriss. p.a.) was obtained from Fluka AG (no. 87369) and distilled before use. The urine samples were furnished by 20 coworkers from our laboratory. The sera were the remains of 20 blood specimens drawn at the University Hospital, Zurich, for routine inves-

Table 1. Selectivity Factors, Detection Limit, Slope of the Electrode Function, and Membrane Resistance of Na^+-Solvent Polymeric Membranes

	Miniaturized electrode based on ligand		Glass membrane electrode
J^{z+}	1	2	$(NAS_{11-18})^a$
	Selectivity factors (log $K^{Pot}_{Na,J}$)		
H^+	0.7	−0.1	3.0
Li^+	−1.7	0.5	−3.0
K^+	−0.4	−2.0	−3.0
Rb^+	−1.0[b]	−2.3	−4.5
Cs^+	−1.5[b]	−2.4	−3.0
NH_4^+	−1.0[b]	−1.7	−4.5
Mg^{2+}	−3.3	−2.2	—
Ca^{2+}	−3.1	−1.5	—
Sr^{2+}	−2.5[b]	−2.0	—
Ba^{2+}	−2.2[b]	−2.3	—
Detection limit (log a_{Na})	−4.6	−5.1	
Slope, mV	57.5 ± 0.1	60.1 ± 0.7	
Range of linear-regression (log a_{Na})	−3.1 to −1.0[c]	−4.1 to −1.0[d]	
Membrane resistance, Ω	$5.4 \cdot 10^7$	$2.1 \cdot 10^7$	

[a] See reference *32*. [b] Values obtained with a macroelectrode (*24*). [c] n = 3. [d] n = 4.

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Received Dec. 30, 1982; accepted May 2, 1983.

tigations. Every serum sample was apportioned into two aliquots, each of which was analyzed by both flame photometry and potentiometry.

Minielectrode System

All EMF measurements were performed on cells of the type: Hg, Hg_2Cl_2; KCl (satd.) | 3 mol/L NH_4Cl | sample || PVC membrane || 0.1 mol/L NaCl; AgCl, Ag.

The external reference electrode was a double-junction saturated KCl/calomel electrode, with a ceramic diaphragm (see Figure 1 and reference *27*). Because the same cell assembly was used for K^+-measurements (*28*), the preferred bridge electrolyte was NH_4Cl instead of KCl [for a discussion of corrections of the liquid-junction potential for different equitransferent electrolytes see (*29*)]. The potential difference between the reference and a Na^+-selective electrode was measured differentially relative to the common electrode (platinum wire), to obtain more stable potentials of the cell assembly.

Two different membranes were examined. One consisted of, per gram, 11 mg of ligand 1, 661 mg of BBPA, and 328 mg of PVC, and the other of 10 mg of ligand 2, 659 mg of BBPA, and 331 mg of PVC. The preparation of PVC membranes and minielectrodes was described in detail earlier by Jenny et al. (*30*).

For the differential measurement of EMF, we prepared a common electrode by inserting a platinum wire into the lumen of a glass capillary tube so that its tip projected beyond the end of the capillary by about 1 mm. The Pt wire was fixed with a two-component resin and soldered to an electrical connector.

EMF Measurements

The minielectrodes (the reference, the common, and one or two Na^+-selective electrodes) were mounted on a novel flow-through measuring cell (see Figure 1) machined from a block of poly(methylmethacrylate). The electrodes were fixed in place with silicone O-ring seals and aluminum retaining sleeves. A polypropylene holder was fixed on this arrangement, to ensure a good mechanical stability. The sample solutions were aspirated with a peristaltic pump (Perpex Modell; H. J. Guldener, Zurich, Switzerland) downstream of the measuring channel, at a flow rate of 18 mL/h. To eliminate electrostatic charging effects, the plastic pump cover touched a metal screen, the Plexiglas and the polypropylene housings were overlaid with thin aluminum foil, and all these metal shields were grounded. All measurements were performed at 21 ± 1 °C. The reference and the ion-selective electrodes were provided with field-effect transistor operational amplifiers (AD 515 KH; Analog Devices, Norwood, MA 02062) and the potential differences were measured relative to the Pt wire common. The analog signal of the difference amplifier (input impedance: 2 pF || 10^{15} Ω) was processed by an analog interface board (DT 1744; Data Translation, Natick, MA) and a single-board computer (SBC 80/20-4; SBC 116 A; Intel Corp., Santa Clara, CA) was used to store the data for further use—e.g., data treatment with the incorporated arithmetic processor (AMC 95/6011; Advanced Micro Computers, Santa Clara, CA). EMF, time, and channel information were punched on paper tape (Facit 4070; Facit AB, Central Service Department, S-59700 Åtvidaberg, Sweden) for off-line processing on a Hewlett-Packard HP-85 calculator system. A display terminal (ADDS Regent 20; Applied Digital Data Systems Inc., Hauppauge, NY 11787) and a printer (Matrix-Drucker Print Swiss; Wenger Print Swiss Matrix, Basel, Switzerland) completed this EMF-measurement device.

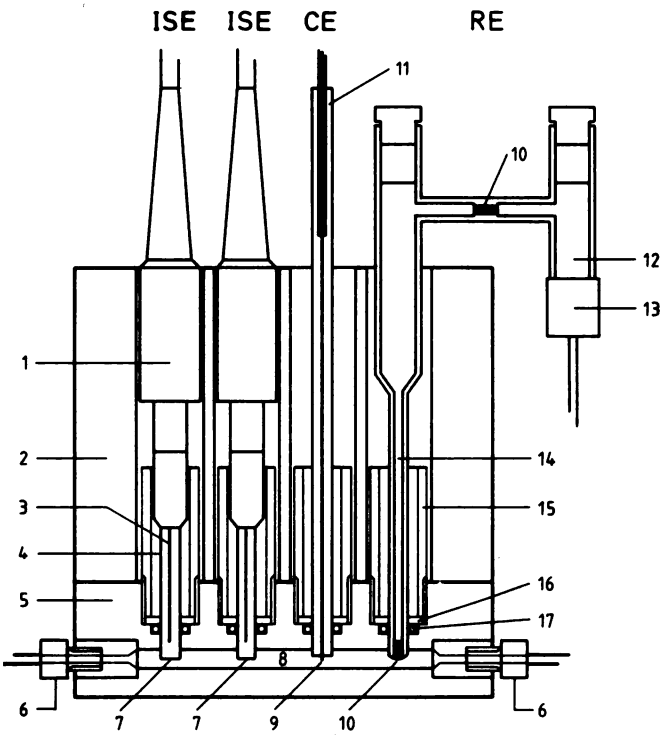

Fig. 1. Schematic cross section of the flow-through electrode system

ISE, miniaturized ion-selective electrode; *CE*, common electrode; *RE*, reference electrode; *1*, impedance convertor; *2*, polypropylene holder; *3*, Ag/AgCl; *4*, PVC tube; *5*, measuring cell; *6*, fittings with PTFE tubing; *7*, Na^+-selective membrane; *8*, sample channel; *9*, Pt wire; *10*, ceramic diaphragm; *11*, glass capillary tube; *12*, reference electrolyte (KCl, satd.); *13*, Hg/Hg_2Cl_2; *14*, bridge electrolyte (3 mol/L NH_4Cl); *15*, aluminum retaining sleeve; *16*, metal ring; *17*, O-ring seal

Selectivity Factors and Electrode Function

The selectivity factors $K^{Pot}_{Na,J}$ (see Table 1) were obtained by the separate-solution method (*31*) with 0.1 mol/L chloride solutions. We measured six pure NaCl solutions (10^{-6} to 10^{-1} mol/L) to determine the electrode functions and the detection limits (*31*). We corrected the experimental EMF values for changes in the liquid-junction potential by using the Henderson formalism (*29*). The activity coefficients were calculated according to the Debye–Hückel formalism and the parameters given in reference *29*.

Procedures

Urine measurements. Before making the urine measurements, we determined the slope of the electrode function three times by measuring three sodium calibration solutions containing 60.0, 100.0, and 180.0 mmol of Na^+ per liter in the presence of, respectively, 40.0, 66.7, and 120.0 mmol of K^+ per liter (all salts as chlorides). The Na^+/K^+ 100.0/66.7 mmol/L solution was then measured alternately with the urine samples. After we finished the urine measurements, we measured the three calibration solutions once more to check the electrode. To reduce cross-contamination of the sample solutions, we injected two columns of air during sample changeover.

The EMF readings were taken every 30 s for 4.5 min. The response times (*31*), however, were considerably shorter (typical response time observed: $t_{90} < 30$ s).

For the urine measurement the evaluation procedure as described for the blood measurements (see equation 5 below) was unsatisfactory. To obtain the sodium concentrations presented in Figure 2, we used a more sophisticated procedure, taking account of the different ionic strengths of the calibration solutions and those of the urine samples. The sodium activity, a_{Na}, of the urine was calculated according

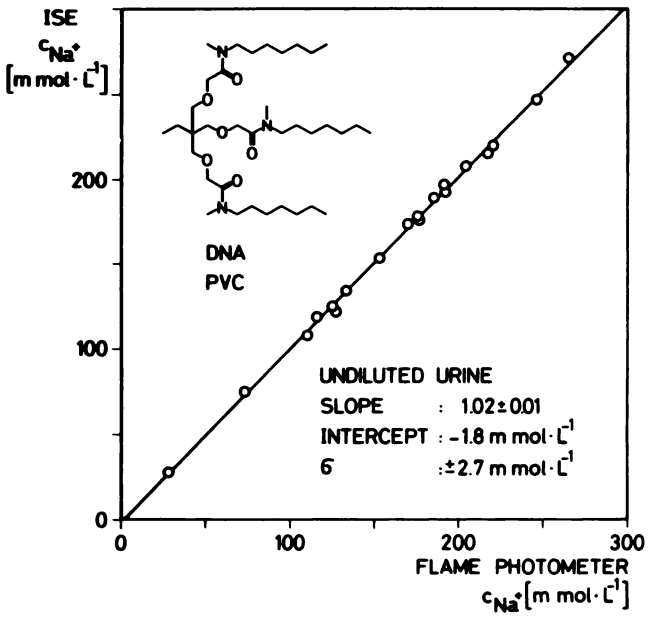

Fig. 2. Correlation of Na^+ measurements in 21 urine samples as obtained by potentiometry (*ISE*, undiluted samples), and by flame photometry (diluted samples)

Linear regression gives the equation for the line: $y = -1.77$ (SD 1.85) + $1.02x$ (SD 0.01). The residual standard deviation of y on x is ± 2.7 mmol/L over the given range

to the Nernst equation, with the mean slope of the electrode, $\bar{s}$, obtained from the three-point activity calibrations, and ΔE, the EMF difference (in millivolts) of the cell assembly between the 100 mmol/L Na^+ calibration solution and the urine sample:

$$a_{Na} = 74.6 \times 10^{-\Delta E/\bar{s}} \quad (1)$$

To calculate a first estimate of the sodium concentration with the obtained activity, we assumed a hypothetical activity coefficient ($\gamma_0 = 0.7$) according to the following equation:

$$c_{Na} = \frac{a_{Na}}{\gamma_{Na}} \quad (2)$$

The sum of this sodium concentration and of the potassium concentration, c_K (determined by flame photometry in this work, but see also ref. *28*), of the urine gave a first ionic strength I:

$$I = 0.5\,(c_{Na} + c_K) \quad (3)$$

which allowed the calculation of a new activity coefficient according to the following relation (*29*):

$$\log \gamma_{Na} = \frac{-A \cdot \sqrt{I}}{1 + B \cdot \sqrt{I}} + C \cdot I \quad (4)$$

where A, B, and C are as given in reference *29*. A new sodium concentration was then calculated from equation 2. This iteration loop was continued two or three times until a constant activity coefficient (and, by implication, a constant sodium concentration) was obtained.

Blood-serum measurements. The procedure for measuring sodium in blood serum was analogous to that for urine. Calibration solutions containing 50.0, 140.0, and 500.0 mmol of Na^+ per liter with an ion background of K^+ (4.0 mmol/L), Ca^{2+} (1.1 mmol/L), and Mg^{2+} (0.6 mmol/L) (all chloride salts) were used to determine the slope of the cell assembly. We measured the 140 mmol/L Na^+ calibration solution between each two blood-serum samples. In contrast to the measurement of urine, the pump was turned off during the EMF data acquisition, to minimize the sample volume. We calculated the $[Na^+]$ in blood serum by the following relation:

$$c_{Na} = 140 \times 10^{-\Delta E/\bar{s}} \quad (5)$$

Flame photometry. We also determined Na with an IL-343 flame photometer (Instrumentation Laboratory Inc., Lexington, MA 02173), mixing the urine or blood serum samples with 1 mol/L LiCl, 1 mol/L Li_2SO_4, and doubly distilled water (1/1/200 by volume). A two-point calibration for Na and K was made after every third sample by using water and a NaCl/KCl solution (0.12 mol/L each). The photometer was operated with a propane/air flame. In a further step, the sodium concentration in blood serum obtained by flame photometry, $c_{Na,f}$, was corrected for the protein and lipid volume. The free-water volume, V_W, in milliliters per 100 mL of blood serum was determined from the following empirical relation (see reference *33*):

$$V_W = 99.1 - 0.73\,c_P - 1.03\,c_{PL} - 0.99\,c_C - 1.09\,c_T \quad (6)$$

where c_P is the total protein concentration (in g/100 mL), c_{PL} is the phospholipid concentration (g/100 mL), c_C is the cholesterol concentration (g/100 mL), and c_T is the triglyceride concentration (g/100 mL). Because of their very low concentration, the free fatty acids were not considered. The other lipid fractions and the protein concentration in blood serum were determined routinely in the Medico-Chemical Central Laboratory of the University Hospital in Zurich. The corrected sodium concentration (in mmol/L) of blood serum, $c'_{Na,f}$, was then calculated with the equation:

$$c'_{Na,f} = 100 \times c_{Na,f}/V_W \quad (7)$$

where $c_{Na,f}$ is the sodium concentration, in mmol/L, determined by flame photometry.

Results and Discussion

Novel membranes composed of ligand 1 or 2, bis(1-butylpentyl)adipate as membrane solvent, and poly(vinylchloride) as membrane matrix have been characterized (see Table 1). The liquid membrane based on ligand 2, as compared with the corresponding membrane with ligand 1, exhibits an improved Na^+/K^+ selectivity and still shows sufficient Na^+/Ca^{2+} selectivity. Therefore throughout this paper we present results obtained with membrane electrodes containing ligand 2.

Figure 2 confirms that results of direct potentiometric Na^+ determinations in urine samples indeed agree well with values obtained by indirect measurements with a flame photometer. For this correlation the residual standard deviation is found to be ± 2.7 mmol/L over the Na^+ range of 20 to 280 mmol/L (correlation coefficient $r = 0.9989$, n = 21). This compares favorably with similar studies with Na_+-selective glass electrodes (*1, 9–11*). Long-term measurements in the outflow of bladder catheters of patients in intensive-care units are under way (*34*).

Using the same membrane, we compared electrode potentiometric measurements in undiluted serum with indirect flame-photometric determinations (Figure 3). The uncorrected results obtained by direct potentiometry and indirect

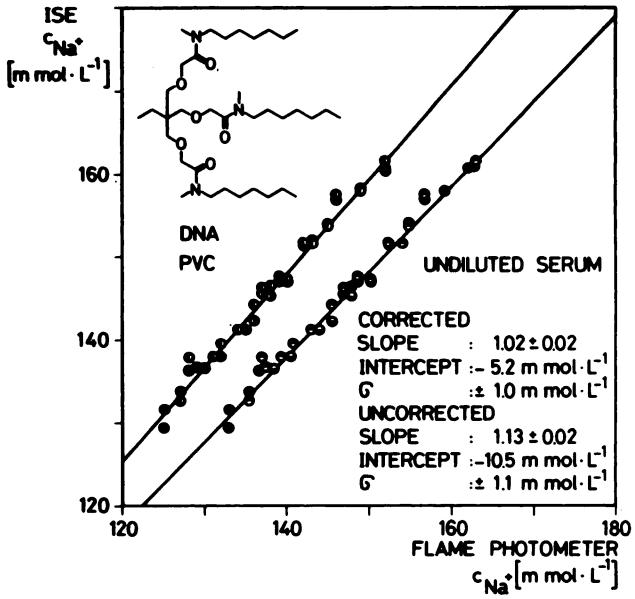

Fig. 3. Correlations between Na^+ measurements in 20 serum samples as obtained by direct potentiometry (*ISE*) and by flame photometry

The 20 serum samples were analyzed twice. First run, [Na^+] uncorrected (◐) and corrected (◓) for protein and lipid volume (see *Materials and Methods*). Second run, [Na^+] uncorrected ◑ and corrected (◒). Linear regression on the uncorrected results (c_{Na} vs $c_{Na,\,f}$) gives the *upper line:* i.e., $y = -10.50$ (SD 2.96) + $1.13x$ (SD 0.02), n = 40. The residual standard deviation of y on x is ± 1.1 mmol/L over the given range. Linear regression on the corrected results (c_{Na} vs $c'_{Na,\,f}$) gives the lower line: $y = -5.15$ (SD 2.51) + $1.02x$ (SD 0.02). The residual standard deviation of y on x is ± 1.0 mmol/L over the given range. *DNA*, bis(1-butylpentyl)adipate; PVC, poly(vinyl chloride)

flame photometry correlated satisfactorily (residual standard deviation 1.1 mmol/L; upper curve in Figure 3). There is, however, a positive bias of about 5% in the electrode results. This is in agreement with corresponding correlations others have obtained with Na^+-glass electrodes (*1–5, 20, 35–40*), although the bias observed here is somewhat larger. Assuming physiological, normal values for proteins and lipids, an empirical relation [see *Materials and Methods, (33)*] predicts a bias of 6.7%. On applying this correction to the measurements discussed here, the lower curve in Figure 3 is obtained, which now deviates from the ideal correlation line by about 1%. This fact was observed and discussed by several authors (*2–5, 16, 20, 37, 41–45*). Besides the correction for protein and lipid volume, the binding of Na^+ to (e.g.) bicarbonate (*20, 43*), to proteins (*44, 46*), to unknown substances (*4, 42*), water binding (*20*), effects at the liquid junction (*45, 47–49*), and calibration and/or evaluation procedure (*2, 16, 20, 45, 47, 49*) have been proposed as further factors to be considered. Calculations using the Debye–Hückel, Henderson, and Nicolsky formalisms and calibration with a 140 mmol/L Na^+ solution make it obvious that, after correction for protein and lipid volume, the negative bias cannot be due to uncertainties in the calibration and evaluation procedure. For a hypothetical sample deviating in the EMF value from this calibration solution by 1 mV one would obtain a bias of less than 0.5% in the Na^+ concentration. This holds even if one uses, ill-advisedly, a reference electrolyte such as 140 mmol/L NaCl, or neglects corrections for changes in the liquid-junction potential or ionic strength, or both.

This work was partly supported by the Schweizerischer Nationalfonds zur Förderung der Wissenschaftlichen Forschung and by Orion Research Inc. Two of us (P.A. and H.-B.J.) thank Rhône-Poulenc and the Swiss Chemical Industry for grants.

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