SHORT COMMUNICATION

Depressed Ionization of Sodium Lactate in Hartmann’s Solution may Cause Free Water Retention
—An in Vitro Study—

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Literatures concerning the use of lactated Ringer’s solution during surgery and for resuscitation of trauma or hemorrhagic shock had been accumulating extensively up until an appeal was raised for moderation in the use of buffered saline solution in patients (Moore, F. D. and Shire, S. T., 1967). Serious morbidity and even mortality were reported following the overenthusiastic use of large volumes of isotonic or hypotonic balanced saline solutions in pre-operative, operative and post-operative patients, as this was found to induce interstitial pulmonary edema (Frank, E. D. 1969; Fleming, W. H. and Bowen, J. C. 1972).

Monafo, Wm. W. (1970) reported the successful use of hypertonic lactated Ringer’s solution in burn patients for the sodium deficit induced by the injury. The hypotonicity of lactated Ringer’s solution has not been discussed as one of the causes of interstitial pulmonary edema.

It is a common concept that sodium lactate is ionized 100% in plasma of which the pH is over 7.0 units, as pK’ of sodium lactate is 3.86 (at 25°C) (Martin, A. W. and Tartar, H. V., 1937). Therefore, it is generally understood that 100% ionization should take place where the pH is 2 units higher than its pK’.

Our repeated measurements of the osmolality of random samples of the lactated Ringer’s solutions on the market elicited without exception lower values than expected. This fact provoked us to attempt to find out if this is caused by hinderance of the dissociation rate of sodium lactate into Na and lactate ions due to the coexistent strong affinity in ionization of sodium chloride.

Authors investigated its dissociation rates in vitro through different ranges of pH and temperature by means of measurement of its specific conductance according to Arrhenius’ law of independent activities of ions (Moeller, T., 1960).

METHOD

1. Preparation of samples
In order to preclude lactone formation from sodium lactate and any chemical contamination in commercially available “Hartmann’s solution”, authors asked Green Cross Pharmaceutical Co. Ltd., Osaka (Japan), to produce solu-
tions as follows:
(a) 27.86 mE/L of pure sodium lactate produced from extrapurified l-sodium lactate and sealed under nitrogen gas;
(b) Doubled concentration, of the former solution;
(c) Double-concentrated, purified Ringer's solution to be used to produce "Hartmann's solution" as \( Na : 205.3 \text{ mE/L, } K : 8 \text{ mE/L, } Ca : 6 \text{ mE/L and Cl : 209.3 mE/L.} \)

By mixing the above solutions in aliquots of (b) and (c), a purified fresh Hartmann's solution was obtained just prior to the experiment.

2. Technical assembly
A schema of the whole assembly of this study is shown in Fig. 1. The specific conductivity was measured by TOA's digital conduction meter, model CM-IDB. Each 25 ml sample was calibrated into a 100 ml beaker which was immersed in a Colora ultra-thermostat water bath temperature controlled to an error limit of within \( \pm 0.01^\circ C \). With the aid of a magnetic stirrer and a disc motor, the sample solution was saturated with nitrogen gas in order to eliminate the effect of carbon dioxide in the air and in the solution. The pH was simultaneously read on TOA's pH-meter model HM-5A and recorded on a titragram, TOA's model EPR-2TB, with an accuracy of \( \pm 0.005 \) unit. The alternation of pHs with graduation per each 0.2 unit from 7.6 to 2.8 was performed by an automatic titrator using IN of HCl with the aid of a pH-stat, TOA's model HS-IB. The expanded volume of the sample due to addition of HCl was corrected on calculation. Technical errors due to calculation were less than \( \pm 5\% \) on the results, being judged by repeated measurements.

3. Theoretical assessments
With titration by HCl, the following chemical process will take place until all sodium lactate is converted to lactic acid.

\[
\begin{align*}
[Na^+] [\text{Lactate}^-] + [H^+] [Cl^-] & \rightarrow [Na^+] [Cl^-] + [H^+] [\text{Lactate}^-]
\end{align*}
\]

Therefore, subtracting a specific conductivity of [NaCl] from the total specific conductivity at any given moment, one can obtain the specific conductivity.
conductivity of the ionized lactate.

Molecular conductivity ($\Lambda$) is calculated as follows from measured specific conductivity ($\kappa$) when a molar concentration ($C$) is known:

$$\Lambda = \kappa / C$$

Then the ratio of ionization ($\alpha$) is obtained by Arrhenius' law of

$$\alpha = \Lambda / \Lambda_0$$

where molar conductivity ($\Lambda$) is divided by its indefinite dilution ($\Lambda_0$). $\Lambda_0$ is calculated from Kohlrausch's law as the sum of each independent ion conductivity ($\Sigma l_0$):

$$\Lambda_0 = l_0^+ + l_0^-$$

Each ion conductivity of indefinite concentration is obtainable from any chemical data book.

Herein, when one changes the temperature of the sample solution, temperature compensation should be applied to each independent ion conductivity.*

By these theoretical considerations, authors obtained the dissociation curves of sodium lactate in pure water and sodium lactate in Ringer's solution at the temperatures of 25°C and 37°C.

4. Osmometry

The sample solution of 0.3 ml and three different brands of Hartmann's solution on the market were checked for their osmotic pressures by Knauer's Halbmikro-ösmometer, type M, applying the freezing point depression method. Measured osmolality was corrected by the osmotic coefficient of 0.931 or 0.932 according to their concentrations and ionic specificity.

Results

The ionization rates ($\alpha$) are presented in Fig. 2. Purified sodium lactate was ionized 100% in the high pHs over 7.0, the difference due to temperature being negligible. Ionization of over 90% was maintained until the pH dropped to 4.8. At around pH 3.9, 50% ionization, the pK' value of sodium lactate, was observed. This pK' value coincided with Martin's report (Martin, A. W. and Tartar, H. V., 1937). On the other hand, the ionization of sodium lactate in Hartmann's solution did not exceed 70% at either temperature even at pH 7.6, although their pK' values were the same as those for purified sodium lactate in water solution.

The calculated osmolality of Hartmann's solution should be 273.8 mOsm/kg for the three brands of Hartmann's solution in clinical use; actually, however, they exhibited osmolalities of 251.8±0.4, 255.2±0.7 and 263.8±0.3 mOsm/kg by our measurements. The values for purified sodium lactate solution were 66.2±0.3 mOsm/kg and for the Ringer's solution used in Hartmann's solution, 207.2±0.2 mOsm/kg. Therefore their sum was 273.4 mOsm/kg, so far as each ingredient was measured separately, and this coincided with the calculated osmolality. However, freshly mixed, purified Hartmann's solution had also exhibited a lowered osmolality of 258.2 mOsm/kg which was within the range of the commercial Hartmann's solutions in clinical use. Meanwhile, as serum osmolality is 286.1±2.4 mOsm/kg on the average.

\* Supposing light-weight molecules of the lactate, sodium, and chloride to be rigid globular particles, one can adopt Stoke's law of conservation of temperature and viscosity to them as follows

$$l_0^{\gamma_i} = l_0^{\gamma_i}$$

where $\gamma_i$ means the viscosity of water at any given temperature of $i$°C. Water viscosity at 37°C has been obtained by Corn's viscosimeter in relative value to the one at 25°C.
pH of solution

Fig. 2 Rate of ionization of Na-lactate on pH changes. Dissociation rate (α) is taken on the ordinate and pH changes on abscissa. The left figure is measured on 25°C as room temperature and on the right 37°C in body temperature’s model.

Discussion

As sodium lactate is a compound of strong and weak electrolytes like other buffers, its ionization cannot be determined by Ostwald’s law of dilution, i.e.:

\[ K = \frac{\alpha^2 C}{(1-\alpha) \times 10^3} \] (8)

because the formula is applicable to strong electrolytes only. The result of depressed dissociation of sodium lactate in Ringer’s solution in this experiment is explained as follows:

Saline, as a strong electrolyte, ionizes in water as follows:

\[ [Na^+] [Cl^-] + [H^+] [OH^-] \]
\[ \rightarrow [Na^+] [OH^-] + [H^+] [Cl^-] \] (a)

while sodium lactate in water is as follows:

\[ [Na^+] [Lactate^-] + [H^+] [OH^-] \]
\[ \rightarrow [Na^+] [OH^-] + [H^+] [Lact^-] \] (b)

When saline and sodium lactate are mixed, it may be:

\[ [Na^+] [Cl^-] + [Na^+] [Lact^-] + 2[H^+] [OH^-] \]
\[ \rightarrow [Na^+] [OH^-] + [H^+] [Cl^-] + \beta [Na^+] [OH^-] + \beta [H^+] [Lact^-] + (1-\beta) [Na^+] [Lact^-] \] (c)

where \( \beta \) means ionized ratio of sodium lactate. The equation (c) will ensue as a result of coexistence of Na ions in both saline and sodium lactate.

The present experiment was carried out in vitro. However, since the major electrolyte in plasma and extracellular fluid is NaCl, a depression of the dissociation of Na and lactate similar to that in vitro is likely to occur in vivo when either sodium lactate or lactate-Ringer solution is given to patients.

As for the fate of unionized sodium lactate in vivo, it can easily be imagined that the unionized molecules of sodium lactate will pass through the cell membrane; consequently swelling of the cells will result. According to our result, as 30% of sodium lactate in Hartmann’s solution
is not ionized, it means that unionized molecules equivalent to over 8.4 mM/L will invade into cellular compartments. This, however, is a modest calculation because the concentration of saline in Hartmann’s solution is 15% lower than that of plasma.

Bertram, F. W. et al. (1967) had introduced about 5 mE/kg of sodium lactate in 0.6 mol solution intravenously into dogs. The exogenous lactate was distributed equally into the total body water, both extra- and intra-cellular fluids. Renal excretion of lactate is relatively low, and its metabolic rate is rather slower than that of pyruvates.

As with a relatively low concentration of 27.86 mE/L of sodium lactate in Hartmann’s solution, no lactone formation can be considered. The unexpected hypotonicity of Hartmann’s solution was assumed to be due to unionized molecules of sodium lactate according to the present experiment.

Fox, C. L., Jr. (1970) preferred the use of sodium acetate-Ringer in burn patients to lactate-Ringer due to his data on urinary output and Na-clearance. Sodium acetate has a higher pK’ of 4.75, and it is easily ionized fully in plasma of pH 7.4. Our unpublished data, however, showed the dissociation of sodium acetate to be 87% also when it was mixed with saline. But it would be better than lactate-Ringer from this point of view, and sodium acetate is easily metabolized by Kreb’s cycle any place in vivo. Our intention is not to object to the use of lactate-Ringer or balanced saline but to point out that attention should be paid to urinary output and free water accumulation when hypotonic solutions are used. A balance in loaded free water becomes particularly difficult in patients with previously compromised cardiac or pulmonary function during major surgeries.

It was a noteworthy fact that the remarkable elevation of ADH was observed in major surgeries in our previous work (Tsuchiya, A. and Fujita, T., 1975).

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References


