Introduction

Electrolyte solutions are widely used in a number of clinical therapies in almost all areas of medicine, with particular importance in intensive care, surgery and the treatment of infections. Despite long experience in the use of single and combined-formula electrolyte solutions, constant progress in this area continues. New ionic formulas are being developed and are in some cases specific for particular situations and diagnoses (1, 2).

Results from recent studies into the use of electrolyte solutions have shown the benefits of a class of solutions which in addition to appropriate proportions of sodium, potassium, magnesium and calcium also contain organic anions such as acetate, malate and occasionally lactate (6, 7, 10). The benefit of such infusion solutions is their ability to compensate fluctuations in the internal environment. This includes “buffering” the physiological acid-base status and ion fluctuations, which can significantly affect physiological functions, such as the potassium/calcium ratio, maintenance of the extracellular volume by sodium content and control of variations in osmolality. Among the most commonly used solutions of this type are the formulations given in Tab. 1.

It is possible that the presence of metabolisable organic anions (e.g. acetate, malate, lactate) could affect oxygen consumption, particularly where the patient receives large volumes of electrolyte solutions during volume resuscitation. This could result in changes in metabolic indicators such as VO₂, VCO₂, resting energy expenditure (REE), etc.

The influence of electrolyte infusion solutions on the intracellular energy state is a largely underestimated parameter, despite the fact that active (endergonic) transport of the majority of ions across the cell membrane is dependent on it (11).

In order to improve this therapeutic approach as much as possible and to obtain reliable clinical data which will allow further development and improvement of infusion solutions, a clinical study has been conducted to investigate the metabolic and energy response to Ringerfundin (B Braun Melsungen AG, Melsungen, Germany) and Plasma-Lyte (Baxter International Inc., Deerfield, USA) in healthy volunteers.

Key words: Electrolytes; Energy expenditure; Infusion solutions

Summary: Measurement of parameters of energy requirement, respiratory quotient (RQ), rate of oxygen consumption (VO₂) and rate of carbon dioxide production (VCO₂) reveal Ringerfundin as an excellent and metabolically stable-acting balanced ionic solution, which does not increase the consumption of O₂ or the total energy requirement. In conclusion, Ringerfundin was very well tolerated and in no case were observed undesirable effects.

Tab. 1: Formulation of tested electrolyte solutions.

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Ringerfundin B. Braun</th>
<th>Plasma-Lyte Baxter</th>
</tr>
</thead>
<tbody>
<tr>
<td>Na (mmol/l)</td>
<td>145</td>
<td>140</td>
</tr>
<tr>
<td>K (mmol/l)</td>
<td>4</td>
<td>5</td>
</tr>
<tr>
<td>Ca (mmol/l)</td>
<td>2.5</td>
<td>-</td>
</tr>
<tr>
<td>Mg (mmol/l)</td>
<td>1</td>
<td>1.5</td>
</tr>
<tr>
<td>Cl (mmol/l)</td>
<td>127</td>
<td>98</td>
</tr>
<tr>
<td>Acetate (mmol/l)</td>
<td>24</td>
<td>27</td>
</tr>
<tr>
<td>Malate (mmol/l)</td>
<td>5</td>
<td>-</td>
</tr>
<tr>
<td>Gluconate (mmol/l)</td>
<td>-</td>
<td>23</td>
</tr>
<tr>
<td>Theoretical osmolality (mOsm/l)</td>
<td>309</td>
<td>295</td>
</tr>
<tr>
<td>Approx. pH</td>
<td>5.5</td>
<td>7.4</td>
</tr>
<tr>
<td>O₂ consumption (l/O₂/l solution)</td>
<td>1.4</td>
<td>4.0</td>
</tr>
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Methods

The clinical conduct of the study was based on a study protocol approved by the State Institute for Drug Control and the local Ethics Committee according to Declaration of Helsinki. It was designed as an open, prospective, monocentre, randomised, crossover comparative study of a single administration of Ringerfundin (B. Braun) and Plasma-Lyte (Baxter) infusion solutions.

Healthy volunteers of either sex aged 18–55 who signed an Informed Consent were included. Before inclusion in the study the volunteers were physically examined and had demonstrated normal ECG, haematology and biochemical parameters. Females were tested for pregnancy. This ensured that they were healthy and did not infringe any of the study exclusion criteria (see Tab. 2).

A total of 14 healthy volunteers were taken into the study that had been randomised on the basis of a list compiled by a pseudo random-number generator. All volunteers completed the study. Both infusion solutions (Ringerfundin B. Braun and Plasma-Lyte Baxter) were administered in a randomised crossover manner. Both administrations were separated by a “wash-out period” of at least one week.

The infusions were administered under stable laboratory conditions. The subjects were in a state of complete rest and under supervision throughout the study. Before the start of the respective infusion the volunteers had been resting on a bed for 2 hours at room temperature. Cannulae were then inserted into both cubital veins and an infusion of the study solution was administered at a rate of 2000 ml over 4 hours using an infusion pump. The infusions were followed by a further two-hour rest period.

The main parameter investigated, i.e. indirect calorimetry, was measured before the start of the infusion (time point 0 h), after 2 hours of infusion (time point 2 h), immediately following infusion (time point 4 h), and finally after another two-hour rest period (time point 6 h). The basic data obtained made it possible to calculate endpoints: resting energy expenditure (REE), the rates of consumption of oxygen (VO₂) and production of carbon dioxide (VCO₂), respiratory quotient (RQ), and utilisation of sugar (Ut_s), protein (Ut_p) and fat (Ut_f).

Blood samples were taken for biochemical and blood gas analysis (Ringerfundin only) before the start of infusion and after completion of infusion.

At 0 and 6 hours urine samples were taken to determine the nitrogen metabolites (creatinine and urea), minerals and osmolality. Additionally, all urine output was collected during the 8 hour period. The quantity and osmolality of the collected urine were measured, and the 8-hour excretion of creatinine, urea and minerals was calculated.

Throughout the study the subject’s clinical condition was constantly monitored and a constant external environment was maintained. The cannulae were removed from the cubital veins at the end of the infusion.

Indirect calorimetry

The principle of indirect calorimetry is based on assessment of energy consumption from the measurement of VO₂ and VCO₂. Exact calculation requires knowledge of the amount of protein catabolised during that period, which is traditionally measured by means of urinary nitrogen (UN) output.

The usual calculation of REE applies Weir’s formula:

\[ \text{REE} = (\text{VO}_2 \times 3.94) + (\text{VCO}_2 \times 1.11) - (\text{UN} \times 2.17) \]

The main components of indirect calorimetry are analysers for expired CO₂ and consumed O₂, and an apparatus for precise measurement of respiratory volumes. In our experiment we used a system based on the canopy application for indirect calorimetry, i.e. the system of open indirect calorimetry with air flow measurement in the mixing chamber. The basic data obtained made it possible to calculate other parameters, such as the REE (9), RQ and the utilisation of individual substrates, e.g. oxidation of sugar, fat and protein. The schematic diagram of the study is shown in Fig. 1. The set-up arrangement for comparing energy requirement in the course of the Ringerfundin and the Plasma-Lyte infusion is shown in Fig. 2.

Biochemical tests

Each biochemical test was conducted using Modular Analytics (Roche Diagnostics, Basel, Switzerland) and CCX (CCX Critical Care Express, Nova Biomedical, Waltham, MA, USA) analysers using the original reagents.

For assays the devices used spectrophotometric analysis methods and ion-selective electrodes.

Review of examinations carried out in the study

The following parameters were examined:

1. Indirect calorimetry: REE - measured resting energy expenditure; REEkg - measured resting energy expenditure per kg of body weight; REEv - calculated resting energy expenditure; RQ - respiratory quotient; Ut_f – fat oxidation; Ut_s – sugar oxidation; Ut_p – protein oxidation.

Table: Tab. 2: Inclusion and exclusion criteria.

<table>
<thead>
<tr>
<th>Inclusion criteria</th>
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<tbody>
<tr>
<td>1. Healthy volunteer aged 18 to 55 of either sex.</td>
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<td>2. Signed informed consent form.</td>
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<table>
<thead>
<tr>
<th>Exclusion criteria</th>
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</thead>
<tbody>
<tr>
<td>1. Febrile disorders in the last 14 days.</td>
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<tr>
<td>2. Use of drugs in the last 14 days, including vitamins.</td>
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<tr>
<td>3. Pregnancy, lactation.</td>
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<tr>
<td>4. Clinical and laboratory signs of inflammation or any other active disorder.</td>
</tr>
<tr>
<td>5. Clinically significant pathological findings in laboratory tests.</td>
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<tr>
<td>6. Abuse – smoking, alcoholism or other substance abuse (smoking in excess of 10 cigarettes per day).</td>
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<tr>
<td>7. Participation in other clinical studies in the last 2 months.</td>
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<tr>
<td>8. Obesity, BMI over 25.</td>
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utilisation; \( U_t_p \) – protein utilisation; \( U_t_s \) – sugar utilisation.
2. Biochemical serum tests: AST, ALT, bilirubin, creatinine, urea, Na, K, Cl, P, Ca, Mg, free ionised Ca, albumin, uric acid, osmolality.
4. Urine biochemistry: creatinine, urea, Na, K, Cl, Ca, P, Mg, including 8 hour output; osmolality.

**Statistics**
The sample size was set on the basis of literature data from comparable clinical studies. For statistical evaluation, the following tests were used: ANOVA, Kruskal-Wallis and One Way Analysis of Variance by Ranks. Statistical evaluations were carried out using SigmaStat 3.1s and SigmaPlot 9.0s software (Systat Software Inc., Point Richmond, USA). A p-value <0.05 was considered significant.

**Results**

**Indirect calorimetry**
Ringerfundin and Plasma-Lyte infusions had no significant effects on VO\(_2\), VCO\(_2\), RQ or REE (Figs 3–6).

The parameters measured by indirect calorimetry at the individual measurement times showed only a slight increase at the second and third measurements, returning to their initial values after completion of the entire planned dose of the infusion solution.

Only the utilisation of proteins, calculated from the non-protein respiratory quotient value, was higher throughout the infusion period in the group receiving the Plasma-Lyte infusion, although this did not exceed the level of statistical significance.
Fig. 4a: Carbon dioxide expenditure during and after Ringerfundin infusion. There is not a statistically significant difference.

\[ \text{VCO}_2 = \text{carbon dioxide expenditure; } A1 - 4 = \text{measurements in time points 0 h, 2h, 4 h and 6 h during and after Ringerfundin infusion} \]

Fig. 4b: Carbon dioxide expenditure during and after Plasma-Lyte infusion. There is not a statistically significant difference.

\[ \text{VCO}_2 = \text{carbon dioxide expenditure; } B1 - 4 = \text{measurements in time points 0 h, 2h, 4 h and 6 h during and after Plasma-Lyte infusion} \]

Fig. 5a: Resting energy expenditure 6h during and after Ringerfundin infusion. There is not a statistically significant difference.

\[ \text{REE} = \text{resting energy expenditure; } A1 - 4 = \text{measurements in time points 0 h, 2h, 4 h and 6 h during and after Ringerfundin infusion} \]

Fig. 5b: Resting energy expenditure 6h during and after Plasma-Lyte infusion. There is not a statistically significant difference.

\[ \text{REE} = \text{resting energy expenditure; } B1 - 4 = \text{measurements in time points 0 h, 2h, 4 h and 6 h during and after Plasma-Lyte infusion} \]
Fig. 6a: Respiratory quotient during and after Ringerfundin infusion. There is not a statistically significant difference. RQ = respiratory quotient; A1 – 4 = measurements in time points 0 h, 2h, 4 h and 6 h during and after Ringerfundin infusion.

Fig. 6b: Respiratory quotient during and after Plasma-Lyte infusion. There is not a statistically significant difference. RQ = respiratory quotient; B1 – 4 = measurements in time points 0 h, 2h, 4 h and 6 h during and after Plasma-Lyte infusion.

Fig. 7: Ionised calcium concentration. There is a statistically significant difference between groups S_CaI Az vs. S_CaI Ak and S_CaI Bz vs. S_CaI Bk.
S_CaI = ionised calcium concentration in serum; A = Ringerfundin; B = Plasma-Lyte; z = before infusion; k = after infusion.

Fig. 8: Urea concentration in serum. There is a statistically significant difference between groups S_UREA Az vs. S_UREA Ak.
S_UREA = urea concentration in serum; A = Ringerfundin; B = Plasma-Lyte; z = before infusion; k = after infusion.
Biochemical serum and urine tests

The serum concentrations of phosphates, sodium, chloride, potassium, uric acid, creatinine, albumin and osmolality as well as plasma pH were not affected by either Ringerfundin or Plasma-Lyte infusions.

The serum ionised calcium concentration increased after infusion of Ringerfundin, while a decrease was observed after Plasma-Lyte. The increase of serum ionised calcium after Ringerfundin was statistically significant (p<0.05) On the whole, the ionised calcium concentrations were in the normal clinical range after treatment with both solutions. (Fig. 7).

An interesting finding was the difference in the bilirubin level. Statistically-significant increase (p<0.05) in serum bilirubin concentration was observed after administration of Plasma-Lyte (11 (9, 17) and 18 (15, 22) μmol/l, respectively), while there was no statistically-significant change after Ringerfundin infusion (9.5 (8, 13) and 15 (12, 18) μmol/l, respectively).

The most significant finding was the statistically significant (p<0.05) decrease in serum urea concentration in the group administered Ringerfundin, while the group receiving the Plasma-Lyte infusion did not reveal any statistically significant change (Fig. 8).

The amount of urine excreted after the Ringerfundin infusion was higher than after the infusion of Plasma-Lyte although the difference was not statistically significant. After 8 h, there was no statistically-significant difference in urinary creatinine or urea, or in urine osmolality. The measured concentrations of minerals in urine were in the normal range.

No adverse events occurred during the clinical study.

Discussion

Progress continues to be made in the development of electrolyte solutions, particularly with their frequent and significant use in patients with clinically severe conditions, or in critical patients after extensive multiple trauma, surgery or in the course of severe infection or even sepsis. The most recent types of balanced electrolyte solutions need to fulfil a whole range of important requirements.

Balanced electrolyte solutions must not only prevent, but in particular also correct deviations in the internal environment in terms of its composition (ion content), pH and volume. With regard to the favourable addition of certain metabolisable anions such as acetate, malate or lactate, it can be expected that the ultimate effect of the administered solution, even in larger volumes, will not unfavourably affect oxygen consumption, CO₂ production or the energy balance.

The new generation of electrolyte solutions applies the metabolism of anions in the form of acetate and/ or malate in preference to lactate. The main disadvantages of lactate are particularly manifested in conditions of impaired microcirculation and hypoxia in the peripheral and visceral tissues. The advantages of a well-balanced crystalloid solution can be summarised as follows:

- it is isotonic and contains all main ions to replenish, balance and restore the internal environment in the required ratio;
- it provides a stable acid-base balance, even in situations of fluctuation towards alkalinity or acidity;
- it is safe even in higher doses – it does not contain an excess of any ion which would result in a disequilibrium syndrome;
- a favourable composition of organic ions makes it possible to keep O₂ consumption and CO₂ production at a minimum even in conditions of impaired tissue perfusion (traumatic shock, septic shock, intoxication) and in conditions of impaired O₂ and CO₂ exchange between the tissues and the external environment.

Rapidly-metabolisable ions such as acetate and malate have many benefits in comparison with the older types of ionic solutions used to achieve equilibrium. In addition to the aforementioned risks of lactate administration in states of hypoperfusion and hypoxia, the administration of bicarbonate destabilises the solution, although it only slightly improves intercellular alkalinisation. A 24 mmol/l acetate content and a 5 mmol/l malate content is equivalent to 34 mmol/l of bicarbonate administration.

The low consumption of oxygen after administration of malate and acetate was shown very well in some studies (5, 8, 13). Even when the entire volume of 2000 ml of the investigational Ringerfundin solution was administered over 4 hours we observed, besides stable resting energy expenditure values, no other changes in energy metabolism (VO₂, VCO₂, RQ).

In theory these findings were also noted in post-lung transplant patients (5). The benefit of acetate from the metabolic aspect has been confirmed by further observations, in both the experimental and clinical setting (3, 8, 14), relating to e.g. conditions during haemodialysis, in the stress of increased gluconeogenesis, and also in relation to muscle metabolism (4, 12).

The following additional phenomena associated with treatment with Ringerfundin were observed:

- When comparing Ringerfundin solution with the control solution (Plasma-Lyte, Baxter), even with strict observance of the rate and total volume of the infusion solution, we noted a decrease of serum urea, which was probably a result of improved urinary excretion of urea after Ringerfundin.
- Measurement of urinary urea production did not indicate any increased protein catabolism.
- After administration of Ringerfundin, even with increased diuresis there was no decline in calcæmia which was observed in the control solution (Plasma-Lyte, Baxter). We regard this as a highly significant phenomenon, because of the detrimental effect of development of hypocalcaemia in some critical conditions.
- There was no significant increase of bilirubin concentra-
tion after administration of Ringerfundin contrary to Plasma-Lyte, although no clear explanation of this phenomenon was found.

- Compared with the control solution (Plasma-Lyte, Baxter), there was greater increase in diuresis after Ringerfundin, although the difference was not statistically significant.

Conclusions

1. Detailed measurements of energy requirement parameters RQ, VO₂ and VCO₂ showed Ringerfundin to be an suitable solution with stable metabolic effect, and a balanced electrolyte solution which does not increase O₂ consumption or the total energy requirement.

2. Ringerfundin solution does not unfavourably affect the ion composition of serum. It does not create ion imbalance and does not affect osmolality when 2000 ml are administered over 4 hours.

3. At the end of the infusion period there was a decrease in serum urea accompanied by a decrease in total creatinine, which however was not statistically significant.

4. The Ringerfundin solution investigated did not lead to calcium depletion.

5. The nitrogen balance estimated from urinary excretion and nutrient substrate measurement by indirect calorimetry did not indicate increased protein catabolism during or after the Ringerfundin infusion.

In conclusion, Ringerfundin was very well tolerated and no adverse events occurred.

Dedication

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References


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