Masterclasses in medicine

Hyponatraemia and hyperglycaemia during laproscopic surgery

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Summary

The aim of this masterclass is to develop a rational plan of therapy to deal with a severe degree of hyponatraemia (90 mmol/l) and hyperglycaemia (100 mmol/l) that occurred 100 min after the start of laproscopic surgery in a young woman. The lavage fluid used in this procedure was 10% dextrose·H₂O in water (505 mmol glucose/l). To focus attention on specific issues, three questions are posed to the reader, as they were to a panel of 59 modern-day experts. Two imaginary consultants from the past were asked the same (and additional) questions. Their responses were restricted to knowledge available before the molecular era, to show the power of integrative physiology at the bedside. An analysis of intracellular events was helpful in answering the first question: ‘Is an infusion of hypertonic saline required to treat her acute hyponatremia?’ Similarly, a quantitative analysis of changes in the composition of the extracellular fluid compartment was helpful in answering the second question: ‘Is an infusion of isotonic saline required to treat her hypotension?’ A metabolic analysis was used to answer the third question, ‘Should insulin be administered?’

Introduction

This is our second article in this series on the application of principles of integrative physiology at the bedside.¹ The central figures are two imaginary consultants, the renal physiologist Professor McCance, and the biochemist Sir Hans Krebs. They deal with data from a real case. Their emphasis is on concepts that depend on an understanding of physiology that crosses the usual subspecialty boundaries. To avoid overwhelming the reader with details, key facts are provided only when necessary. The overall objective is to demonstrate how the application of simple principles of integrative physiology can play an important role at the bedside (Table 1).

The consultation focuses on an evaluation of two profound abnormalities, hyponatraemia and...
Table 1  Summary of physiology principles

<table>
<thead>
<tr>
<th>Physiology principle</th>
<th>Comment</th>
</tr>
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<tbody>
<tr>
<td>1. Control of cell volume depends on water permeability and the effective $P_{\text{osm}}$</td>
<td>Cell membranes have water channels</td>
</tr>
<tr>
<td>2. Glucose is an effective osmole if glucose transport is a rate-limiting step</td>
<td>Effective osmolality = $2 \times (P_{\text{Na}}) + P_{\text{Glu}}$ in mmol terms</td>
</tr>
<tr>
<td>3. The ECF volume is determined by the number of effective osmoles in the ECF and the $P_{\text{osm}}$</td>
<td>Glucose diffuses rapidly in and out of hepatocytes</td>
</tr>
<tr>
<td>4. The plasma (arterial) volume is the most important component of the ECF</td>
<td>Glucose transport is a slow step in skeletal muscle and across the BBB</td>
</tr>
<tr>
<td>5. Mass balance must be assessed to explain a change in effective $P_{\text{osm}}$</td>
<td>Na$^+$ deficit = contracted ECF volume</td>
</tr>
<tr>
<td>6. Actions of insulin that may lead to a fall in the $P_{\text{Glu}}$</td>
<td>ECF volume expansion causes hyponatraemia if water balance is positive or if hypertonic glucose is added</td>
</tr>
<tr>
<td></td>
<td>The CVP is a more relevant physiological parameter than the venous volume</td>
</tr>
<tr>
<td></td>
<td>Assess intake and output of water and effective osmoles as separate entities</td>
</tr>
<tr>
<td></td>
<td>Oxidation: this requires fuel selection ('do not burn fat'); its upper limit set by the rate of ADP formation or $O_2$ consumption during exercise</td>
</tr>
<tr>
<td></td>
<td>Conversion to the storage forms, glycogen and triacylglycerols</td>
</tr>
</tbody>
</table>

ECF, extracellular fluid; CVP, central venous pressure; BBB, blood-brain barrier.

hyperglycaemia. When each element is analysed in a quantitative fashion, the therapeutic plan becomes more credible. The reader can compare their choices for therapy with those from a panel of experts and with our imaginary consultants. We stress that there are no absolute answers to the questions posed.

The consultation

You are asked to help plan therapy for a 32-year-old, 50-kg woman who underwent elective laparoscopic surgery to remove a uterine fibroid that morning. She received the usual 2 l of isotonic saline intravenously to maintain her blood pressure during anaesthesia. The lavage fluid was 10% dextrose,$H_2$O in water (505 mmol glucose/litre). No problems were anticipated because she was previously healthy, there was no family history of diabetes mellitus, and she did not take medications. Moreover, her pre-operative blood tests for glucose, creatinine, sodium (Na$^+$), and potassium (K$^+$) were in the normal range.

Approximately 90 min after the procedure began, ventricular tachycardia developed and her blood pressure fell to 90/40 mm Hg. With initial management for this emergency, her blood pressure returned to normal. Blood drawn at this time revealed two striking abnormalities: her plasma Na$^+$ concentration ($P_{Na}$) was 90 mmol/l and her plasma glucose concentration ($P_{Glu}$) was 100 mmol/l (1800 mg/dl). Her plasma K$^+$ concentration ($P_k$) was 4.2 mmol/l. There was no other pertinent information. The presumptive diagnosis was that an unknown volume of this lavage fluid entered her body through uterine veins cut during surgery.

The reader is asked to focus only on the changes in her $P_{Na}$ and $P_{Glu}$. The three major questions that will be asked were also sent to a number of specialists in international academic centres, and their responses will be revealed later. The questions are, first, should hypertonic saline be given to treat her $P_{Na}$ of 90 mmol/l—if yes, how much would you give in the next hour? Second, is hypotension a good reason to give isotonic saline—if yes, how much would you give in the next hour? Third, is it prudent (or dangerous) to give her insulin—if yes, how much would you give in the next hour and by what route? We ask the reader to pause and consider these questions.

The need to administer hypertonic saline as revealed by anticipated changes in her ICF volume

Everyone on the medical team was confident that they were dealing with acute hyponatraemia, because her $P_{Na}$ was normal prior to anaesthesia. They were also aware that the intracellular fluid (ICF) volume is usually expanded during acute hyponatraemia (Figure 1). Moreover, because the brain is in a closed space (the skull) and close to 80% of its weight is water, with two-thirds of this water in brain cells, there is very little opportunity
to accommodate brain cell swelling without a large rise in intracranial pressure. Based on this information, the concern was that this patient might die due to herniation of her brain through the foramen magnum. Hence it seemed reasonable to administer hypertonic saline (NaCl) to decrease her brain cell volume. A similar conclusion was reached by 26/59 of the specialists who participated in our survey (Table 2). However, one glance at the frown on the countenance of Professor McCance was enough to produce a sudden loss in enthusiasm for this mode of therapy. We ask the reader to pause and consider, ‘What was the flaw in the logic concerning the use of hypertonic saline?’

Question 1: What was the flaw in the logic concerning the use of hypertonic saline?

**Physiology principle 1: control of cell volume**

Two factors influence cell volume. First, water can diffuse rapidly across cell membranes because they have water channels. Second, the driving force for water movement is a difference in effective osmotic pressure across cell membranes. The major effective solute in the ECF compartment is Na⁺, while the effective solutes in the extracellular fluid (ECF) compartment are Na⁺ plus the monovalent anions chloride (Cl⁻) and bicarbonate. Urea is not an effective osmole, because there are urea transporters in all membranes. The number of effective intracellular osmoles is constant with a few exceptions, such as in brain cells during chronic hyponatraemia (decrease in number of ICF solutes) or skeletal muscle during a seizure or with rhabdomyolysis (increase in number of ICF solutes).

**Figure 1.** Water movement across cell membranes. The solid circle represents a cell membrane with a normal cell size and the dashed circle swollen cells with hyponatraemia. There are water channels (aquaporins, AQP) to facilitate water diffusion (open circle). The effective osmoles are Na⁺ salts and glucose in the ECF compartment and K⁺ for the most part in cells. Cells swell when the effective osmolality of the ECF declines because the number of effective osmoles in the ICF compartment tends to be constant in most organs (P = ICF effective osmoles).

The consultation synopsis from this patient was sent to 59 medical specialists who deal with hyperglycaemia and/or hyponatraemia. The data represent the number of physicians who would have given hypertonic saline, isotonic saline and/or insulin at the 100-min time and after the cardiac arrhythmia was successfully treated. ICU, intensive care unit.

<table>
<thead>
<tr>
<th>Medical specialty</th>
<th>Treatment</th>
<th>Hypertonic saline (Yes/No)</th>
<th>Isotonic saline (Yes/No)</th>
<th>Insulin (Yes/No)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Endocrinologists</td>
<td>3/7</td>
<td>6/4</td>
<td>6/4</td>
<td></td>
</tr>
<tr>
<td>ICU physician</td>
<td>5/5</td>
<td>7/3</td>
<td>6/4</td>
<td></td>
</tr>
<tr>
<td>Nephrologist</td>
<td>18/21</td>
<td>26/13</td>
<td>17/22</td>
<td></td>
</tr>
<tr>
<td>All</td>
<td>26/33</td>
<td>39/20</td>
<td>29/30</td>
<td></td>
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While all the housestaff were persuaded by the logic of their revered renal physiologist, they asked, ‘Might some of her cells be swollen because of hyponatraemia?’ We ask the reader to pause and answer this question.

**Question 2: Might some of her cells be swollen because of hyponatraemia?**

**Physiology principle 2: distribution of glucose**

Glucose is an effective osmole if its concentration is considerably higher in the ECF than in the ICF compartment. Glucose can diffuse readily across cell membranes only if a transporter with sufficient activity facilitates this process.

**Return to the bedside.** All eyes were now on Professor Krebs. He speculated that glucose transporters would not be identical in all organs—their properties should depend on the metabolic function of each organ (Figure 2). Later, it would be shown...
that the molecular and kinetic properties of glucose transporters were unique in different organs.

(i) **Size of her liver cells**: Professor Krebs predicted that liver cells would not have a concentration of glucose that differed appreciably from the $P_{\text{Glu}}$, because hepatocytes must take up glucose rapidly in the fed state and release this brain fuel quickly during fasting. This deduction was later supported by molecular studies—this hepatic glucose transporter is called GLUT-2. He concluded by stating that glucose is not an effective osmole (tonomole) in the liver, and thus does not influence water distribution across hepatocyte cell membranes. Hence with hyponatraemia (and a normal or elevated $P_{\text{Glu}}$), liver cells should be swollen (Figure 2).

(ii) **Size of her skeletal muscle cells**: Because the glucose transport system in muscle (GLUT-4) has a relatively low flux capacity, the concentration of glucose is lower in the ICF than in the ECF compartment of muscle. Unknown to Professor Krebs, the concentration of glucose in the ICF of muscle cells can rise appreciably when insulin levels rise. Therefore glucose should be an effective osmole for skeletal muscle (50% body water) in states when stress hormones are present, because $\alpha$-adrenergic actions inhibit the release of insulin from $\beta$-cell of the pancreas. Hence there are two opposing osmotic forces likely to operate in her muscles. First, muscle cell volume should increase due to hyponatraemia. In contrast, muscle cell volume should decrease due to hyperglycaemia if her insulin levels were not very elevated. In quantitative terms, because these two opposing forces are virtually equal (calculated $P_{\text{osm}}$, 280 mOsm/kg H$_2$O, equation 1), her muscle cells should not be appreciably changed in size. He concluded by stating that because her effective $P_{\text{osm}}$ had been elevated due to hyperglycaemia in a state where high insulin levels were unlikely, skeletal muscle cell volume should be decreased (Figure 2).

(iii) **Size of her brain cells**: The rate-limiting step for glucose movement into the brain is the blood-brain barrier (BBB). Because the BBB is very permeable to water, the effective osmolalities should be equal in her plasma and intracerebral ECF compartment (the cerebrospinal fluid compartment). Moreover, given the saturable transport system for glucose and the short duration of events, the nature of the effective osmole may differ in these two brain compartments (Figure 3). The $P_{\text{Na}}$ will be lower and the $P_{\text{Glu}}$ will be higher.

![Figure 2](image-url)
than corresponding concentrations in the brain ECF compartment. Conceivably, the Na\(^+\) concentration might be close to normal in the ECF of the brain if its glucose concentration has not yet risen appreciably. Nevertheless, her current brain cell size should be close to normal.

One of the bright young physicians was clearly thinking ahead and asked, ‘Should there be an ‘expected degree of hyponatraemia’ when the PGlu is 100 mmol/l?’ We ask the reader to pause and consider their response to this challenging question.

Question 3: Should there be an expected P\(_{Na}\) when the P\(_{Glu}\) is 100 mmol/l?

Corollary to physiology principle 1: control of the ECF volume

The P\(_{Na}\) is dependent on two factors, the total ECF Na\(^+\) content and the volume of the ECF compartment.

Return to the bedside: There are two ways to answer question 3: with data or by theoretical calculation. When relying on data, the conditions of the experiment must match the setting for the patient exactly. Perhaps this is why the data in the modern literature relating the P\(_{Glu}\) to the P\(_{Na}\) are quite heterogeneous.\(^{13}\) Therefore Professor McCance turned to a theoretical analysis. He made the following assumptions for ease of mathematics—first, the normal ECF volume in our 50 kg patient is 10 l (containing 1400 mmol Na\(^+\)). Second, with the net addition of an isotonic glucose solution, there would be no water shift across the ECF:ICF interface, because there was no change in the effective P\(_{osm}\)—the driving force for water movement (Figure 1). He then sketched out two scenarios where the P\(_{Glu}\) would be 100 mmol/l.

In the first scenario, he added an isosmotic glucose solution (285 mmol/l). By adding 5.4 l of this imaginary solution, the P\(_{Na}\) would be 91 mmol/l (1400 mmol Na\(^+\) now dissolved in 15.4 l of ECF), because an isosmotic glucose solution would be distributed solely in the ECF compartment, providing that glucose was not metabolized.

Second, Professor McCance calculated what the P\(_{Na}\) would be if glucose without water was added to the ECF compartment. This addition of hypertonic glucose would cause water to shift from the ICF to the ECF compartment. In this calculation, the P\(_{Glu}\) could also be 100 mmol/l if 1200 mmol of glucose was added, and the P\(_{Na}\) would be 112 mmol/l (Table 3). Therefore there is not a fixed relationship between the rise in P\(_{Glu}\) and the fall in P\(_{Na}\).

Recommendation of Professor McCance: Because her calculated effective P\(_{osm}\) was virtually normal, hypertonic saline was not required, as she was very unlikely to have a significant degree of brain cell swelling (reasons akin to the rationale for near-normal skeletal muscle size in our patient, Figure 2). He added that because the net effective osmolality of the added glucose solution is not known in almost every patient with hyperglycaemia, clinicians should not believe that there is an ‘expected’ value for the P\(_{Na}\) for a given P\(_{Glu}\).

The need to administer isotonic saline, as revealed by anticipated changes in her ECF volume

Isotonic saline should be given to re-expand a contracted ECF volume or to treat a low blood pressure that is due to a low effective arterial volume. Therefore the quest is to evaluate her effective blood volume. Professor McCance emphasized the following points derived from physiology principle 1. First, Na\(^+\) is primarily distributed in the ECF compartment. Second, if there is no change in the effective P\(_{osm}\), there will be no net shift of water across cell membranes. Therefore when an isotonic saline solution is retained, it will simply expand the ECF volume and not influence the ICF volume or composition. At this point everyone wanted to know, ‘How can you determine what the new ECF volume is in our patient?’
Question 4: How can you determine what the new ECF volume is in our patient?

Physiology principle 3: determinants of the ECF volume

The ECF volume is a function of the change in content of the number of effective ECF osmoles, Na\(^+\) and glucose. The effective P\(_{\text{osm}}\) could also influence the ECF volume, but this need not be considered in our patient, because her calculated non-urea P\(_{\text{osm}}\) was virtually normal (equation 1). Therefore separate balances for Na\(^+\) plus glucose will indicate how much her ECF volume differed from normal.

*Return to the bedside*: Balances will be calculated by assessing the input (known) and the output (estimated values).

(i) Na\(^+\) balance: The input of Na\(^+\) in this patient was 300 mmol of Na\(^+\) (2 l of isotonic saline given during the procedure). Her output of Na\(^+\) should occur primarily in the urine. Because there were no measured values, our Professor made the following deduction. The usual concentration of Na\(^+\) in a glucose-induced osmotic diuresis is close to 50 mmol/l.\(^{14}\) As detailed below in the glucose balance section, her maximum urine volume was 2 l, so only 100 mmol of Na\(^+\) could be excreted during an osmotic diuresis. Therefore, 100 min after surgery began, her balance for Na\(^+\) was positive by at least 200 mmol. Thus if the patient had a normal P\(_{\text{Na}}\) before therapy, the only way to develop hyponatraemia would be by dilution, the retention of a large volume of an isosmotic glucose solution.

New ECF volume
\[
\text{ECF volume} = \frac{\text{Total ECF Na}^+ \text{ content (1600 mmol/l)}}{\text{P}_{\text{Na}} (90 \text{ mmol/l})} = 17.8 \text{ litres}
\]

(ii) Glucose content in her ECF compartment: There are two ways to perform this calculation.

First, if the input and output of glucose were known, a glucose balance could be calculated. Since he did not know either of these parameters, Professor McCance relied on a second line of reasoning. He used the Na\(^+\) balance data and the P\(_{\text{Na}}\) to deduce the new ECF volume (equation 2). When this was done, her calculated ECF volume had risen by close to 8 l to 17.8 l. It follows that the quantity of glucose retained in her ECF compartment is the product of her new ECF volume (17.8 l) and her P\(_{\text{Glu}}\) (100 mmol/l) or 1780 mmol. The vast majority of this glucose undoubtedly came from lavage fluid that had entered her body. This conclusion led to a further question for Professor McCance. *Does the fact that her ECF volume was greatly expanded mean that isotonic saline should not be given to this patient?* We ask the reader to pause and answer this question. Professor McCance interrupted his analysis of the glucose balance data to consider this question.

Question 5: Does the fact that her ECF volume was greatly expanded mean that isotonic saline should not be given to this patient?

Physiology principle 4: importance of the effective ECF volume

The ECF volume has two components, a vascular and an interstitial volume. The vascular volume is biologically more important, because it is more directly related to ensuring a sufficient delivery of oxygen to meet the metabolic demands. To deliver oxygen, pressure is more critical than volume.

*Return to the bedside*: Our patient was given the 2 l of saline to combat the hypotensive effect of anaesthetic agents.\(^{15}\) This hypotension is the result of dilution of the veins which lowers the
venous return. Hence the venous volume was expanded to maintain the central venous pressure (CVP).

In summary, Professor McCance said that if he had all the above information and time to perform the calculations, he would not infuse isotonic saline, because he believed that her ECF volume was greatly expanded and there was no haemodynamic emergency once her cardiac rhythm had returned to normal. This view differed from the 39/59 modern-day specialists who chose to give isotonic saline.

On reflection, our Professor had second thoughts about his decision. He wondered out loud: to have a PGlu of 100 mmol/l in a volume of close to 18 l, the patient now had close to an extra 1700 mmol of glucose in her body (her PGlu rose by 95 mmol/l, but a value of 100 mmol/l was used for convenience in equation 3a). To infuse close to this amount with D10W (505 mmol of glucose/litre), she would need an infusion of approximately 3.5 l of D10W over 100 min with an average infusion rate of 35 ml/min (equation 3b). Moreover, a higher infusion rate would be needed if the duration of the leakage of D10W were -100 min and/or if some of the glucose was metabolized or excreted in the urine. Thus the need for these high infusion rates made him uncomfortable with his initial calculations.

\[
\text{Initial body glucose} = 10 \times 5 \text{ mol/l} \\
= 75 \text{ mmol}
\]

\[
\text{New body glucose} = 18 \times 100 \text{ mmol/l} \\
= 1800 \text{ mmol}
\]

\[
\text{Glucose infused} = 3.5 \times 505 \text{ mmol/l} \\
= 1775 \text{ mmol}
\]

**The need to administer insulin as revealed by an analysis of metabolic issues**

The need to administer insulin seemed to be obvious, but was insulin really needed? Before he could address this question, a puzzled medical student raised her hand and asked, ‘How could the \( P_{\text{osm}} \) in our patient be less than normal if the basis for hyperglycaemia was the addition of hyperosmolar glucose (505 mOsm/kg \( H_2O \))?’

**Physiology principle 5: maintenance of a constant \( P_{\text{osm}} \)**

The \( P_{\text{osm}} \) will be constant if the net balances of inputs and outputs have a similar osmolality to the body.

*Return to the bedside:* If the fluid administered was both large in volume and hyperosmolar, it follows that glucose (or some other osmole) must be removed from the body without water. Two potential options for this form of glucose removal are via an osmotic diuresis or by metabolism.

(i) **Removal in an osmotic diuresis:** To be excreted in the urine, glucose must be filtered. The filtered load of glucose is equal to the product of the glomerular filtration rate (GFR) and the PGlu. Because the normal GFR is close to 6 l/h or 10 l/100 min, 1000 mmol of glucose could be filtered in 100 min. Moreover, a normal kidney can reabsorb 10 mmol of glucose per litre of GFR (100 mmol in 100 min), 900 mmol of glucose could be excreted in this time interval (equation 4). With a urine osmolality in the 450 mOsm/kg \( H_2O \) range and if all the osmoles were glucose, the urine volume would have to be close to 2 l.

\[
\text{Glucose excreted} = \frac{\text{Filtered}}{\text{reabsorbed glucose}}
\]

This notwithstanding, it is not clear from the data just how long the PGlu was 100 mmol/l and if the GFR was 6 l/h for the entire 100 min (she was very hypotensive for at least 10 min). More likely, the extremely high PGlu occurred only near the 100-min time point, so total glucosuria might have been much less than 900 mmol.

To achieve a normal \( P_{\text{osm}} \), we should only be concerned with glucose in the urine in hypertonic form (i.e. >285 mOsm/kg \( H_2O \)). With a maximum Uosm of 450 mOsm/kg \( H_2O \) in a high-flow osmotic diuresis, only 1/3 of the osmoles (glucose) are excreted in a hypertonic form. Therefore only 2×150 or 300 mmol of glucose could be removed in hypertonic form in 2 l of osmotic diuresis. Professor Krebs was then asked to deal with metabolic issues.

(ii) **Glucose removal by metabolism:** The first step is to define how much glucose needs to be removed by metabolism (Figure 4). Professor McCance had established that the positive balance for glucose was close to 1800 mmol if its entire
distribution was in the ECF compartment (equation 3a). Because of the need to convert this infused glucose (505 mmol/l) to an isotonic solution (final Posm 280 mOsm/kg H2O), for every 505 mmol of glucose infused, 225 mmol (505/C0) were removed in hyperosmolar form (without water). This means that the total glucose infused was 3246 mmol (equation 5).

\[
1800 \text{mmol} \times \left(\frac{505}{280}\right) = 3246 \text{mmol glucose infused}
\]

To administer 3246 mmol with a concentration of glucose of 505 mmol/l, the total volume infused would have to be close to 6.5 l. Moreover, approximately 1450 mmol (3246–1800 mmol) had to be removed via the osmotic diuresis in hypertonic form and/or by metabolism. If glucosuria could remove only 300 mmol of glucose in hypertonic form, more than 1000 mmol of glucose must be removed by metabolism.

**Physiology principle 6: actions of insulin to lower the PGlu**

There are two major ways insulin can cause glucose to be removed by metabolism. First, insulin can cause glucose to be oxidized by removing the alternate fuel, fatty acids. Second, insulin can augment the synthesis of energy storage forms, glycogen and triacylglycerols.

**Return to the bedside:** Professor Krebs quickly discounted glucose oxidation as an option to remove close to 1000 mmol of glucose in 100 min for three major reasons. First, the usual oxygen consumption in a normal resting human adult is 12 mmol/min. With a stoichiometry of 6 mmol oxygen/mmol of glucose (equation 6), the maximal rate of glucose oxidation would be 200 mmol/100 min. Second, fat mobilization is unlikely to be completely suppressed during the stress of surgery, so some fatty acids and less glucose will be oxidized. Third, he suggested that less glucose would be consumed because the work in the brain (anaesthesia) and muscle (no contraction) is reduced in an anaesthetized person.

\[
\text{Glucose} + 6\text{O}_2 \rightarrow 6\text{CO}_2 + 6\text{H}_2\text{O}
\]

Professor Krebs then considered conversion of glucose to energy stores as a means for glucose removal. First, fatty acid synthesis from glucose is always a very slow process. Second, glycogen synthesis could cause the removal of 1000 mmol of glucose if the appropriate hormonal signals were present. There are two sites of glycogen synthesis to consider; each has an independent control system. Because the entire glycogen pool size in liver is only 600 mmol, if a minimum of 1000 mmol of glucose were removed by metabolism, glycogen synthesis would have to be stimulated predominantly in skeletal muscle. Moreover, the rate of glycogen synthesis would have to be rapid.

**Summary:** Because Professor Krebs doubted that this amount of glucose could be removed by metabolism in this time frame, he wondered whether one of his assumptions was incorrect. We ask the reader to pause and consider, ‘What factor might need to be amended to understand the basis for her severe degree of hyperglycaemia?’

**Question 7:** What factor might need to be amended to understand the basis for her severe degree of hyperglycaemia?

Professor Krebs considered whether the PGlu and PNa might not represent steady-state values because hypotension was present for the last 10 min. Taking an extreme position, some D10W was infused and much of its glucose disappeared, generating osmole-free water. Shortly before her cardiac arrest, D10W continued to be infused, but now perhaps the hyperglycaemia was due to infused D10W that was distributed primarily in the plasma volume of 2.5 l. To raise the PGlu by 100 mmol/l in 2.5 l, 250 mmol of glucose must be added, so the volume of D10W needed would now be close to 0.5 l. Nevertheless, the actual volume of lavage fluid that entered...
her body was likely much larger than 0.5 l, but much less than the estimate of 6.5 l, because of a non-steady-state condition.

Summary: Because the D10W infusion was stopped, a sudden fall in the $P_{\text{Glu}}$ could be anticipated when glucose was diluted in the entire ECF volume and Professor Krebs was therefore reluctant to administer insulin immediately. With a good cardiac output, glucose would also be excreted rapidly by the kidneys.

He added two notes of caution concerning insulin administration. First, if insulin caused glucose to disappear rapidly by metabolism, the retained D10W ($P_{\text{osm}}$ 280 mOsm/kg H2O) could be converted to osmole-free water. Moreover, if this were a large volume, hyponatraemia with a low $P_{\text{osm}}$ would develop, and brain cell swelling could become a new risk factor. Second, there is a danger associated with an intravenous bolus of insulin, because high plasma insulin concentrations can cause K+ to shift into cells.20 While a shift of K+ into cells is appropriate physiology when K+ is consumed, it can lead to hypokalaemia and possibly induce a cardiac arrhythmia when there is no K+ intake.

Professor McCance stated that he too favoured the possibility of a smaller infusion of glucose and therefore changed his mind about the degree of ECF volume expansion. He was less dogmatic about not infusing isotonic saline.

Course in hospital: The patient was treated with hypertonic and isotonic saline. She was given insulin to treat her hyperglycaemia. She developed a marked rise in her $P_{\text{Na}}$ to a peak of 155 mmol/l and a dramatic fall in $P_{\text{K}}$ to 1.9 mmol/l. Unfortunately, she died after another cardiac arrest.

Conclusions

The primary modes of therapy recommended for our patient were to deal with the cardiac arrhythmia and to stop the administration of D10W lavage fluid. To answer the three questions, the most important initial step was to calculate the $P_{\text{osm}}$ due to glucose and electrolytes. Because this $P_{\text{osm}}$ was normal, and if glucose is an effective osmole for brain cells, an appreciable change in brain cell volume was unlikely. This was why hypertonic saline was not our recommended therapy for her acute hyponatraemia. This hyponatraemia is akin to hyponatraemia seen after a transurethral resection of the prostate with isosmotic sorbitol or mannitol-containing lavage fluids.21 The next step in the analysis was to estimate the expected ECF volume. Because the patient might have both a positive balance for Na+ and the addition of a large number of effective osmoles in the form of glucose, her ECF compartment volume could have been expanded by a considerable amount. Therefore if she did not have a haemodynamic problem once her cardiac rhythm was restored, a rapid infusion of isotonic saline was probably not required. Because insufficient glucose could be removed in hypertonic form by an osmotic diuresis or by metabolism, Professor Krebs speculated that the volume of D10W that was infused might be much less than expected. While one could easily be persuaded to give insulin because of the elevated $P_{\text{Glu}}$, Professor Krebs was reluctant to do so for two reasons. First, the $P_{\text{Glu}}$ might fall promptly by dilution once the glucose infusion was stopped and glucose entered the interstitial compartment. Second, a bolus of insulin could produce a severe degree of hypokalaemia. There were also other potential dangers such as acute hyponatraemia and delayed hypoglycaemia.

References

M.R. Davids et al.


