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SPECIAL REPORT

Treatment of hyperglycaemia in diabetic ketoacidosis: natura non facit saltus

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ABSTRACT

In the treatment of severe diabetic ketoacidosis the gradual correction of glucose, electrolyte and fluid derangements is of utmost importance. In this paper the authors provide practical recommendations for these corrections based on novel pathophysiological insights.

KEYWORDS

Diabetic ketoacidosis, hyperglycaemia, hyponatraemia

INTRODUCTION

One of the most challenging parts of the treatment of severe diabetic ketoacidosis (DKA) is to gradually correct the glucose, sodium and fluid disturbances. Osmotic shifts before and even more so during treatment play a crucial role in the development of cerebral oedema, the most dreaded complication of DKA. Although it only seldom occurs in adults, due to its often devastating clinical course with a high mortality (25%) and severe neurological sequelae (35-40%), a substantial part of the treatment is focussed on its prevention.

Several guidelines provide recommendations with regard to glucose, electrolyte and fluid management. Nevertheless, in daily practice treatment of patients with severe DKA continues to generate a lot of discussion. The main topics are:

- What is the optimal rate of glucose correction?
- What is the main parameter that should be used to guide therapy?
- What increase in sodium is acceptable?

Therefore, in this special report, we will illustrate this problem with one case history, provide some pathophysiological background and discuss these issues.

CASE

A 51-year-old woman presented to the emergency department with polydipsia, polyuria, vomiting and diarrhoea. She had lost 6 kg of weight in one week. Her medical history was unremarkable and she was not on any medication. Physical examination revealed a somnolent patient with Kussmaul breathing, a blood pressure of 97/76 mmHg and a pulse of 75/min. Her laboratory results are presented in *table 1*. She had severe acidaemia, due to a combination of ketoacidosis, lactic acidosis and renal failure. Her severe hyponatraemia was probably caused by hyperglycaemia and volume depletion. Furthermore, in the days before admission the patient had drunk large amounts of glucose-containing fluids and water.

The physician at the emergency department had started suppletion with isotonic fluids (NaCl 0.9%), and administered a bolus of insulin, followed by continuous insulin infusion. She was admitted to the intensive care unit. *Figure 1* shows the course of the glucose concentration and the effective serum osmolality. After three hours insulin administration was reduced and the isotonic fluid (NaCl 0.9%) was switched to hypotonic fluid (NaCl 0.65%). In the next 24 hours the serum glucose, electrolytes and anion gap normalised rapidly and the acidaemia disappeared. She felt better and was transferred to the department of internal medicine.

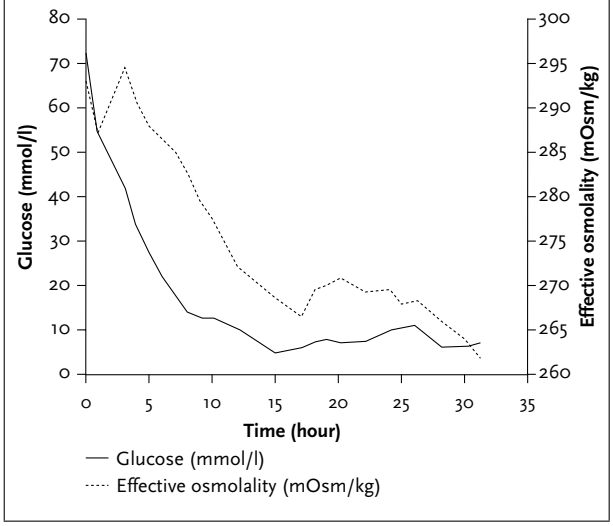
DISCUSSION

The glucose concentration of our patient decreased very quickly, 30 mmol/l in three hours. This was compensated by an increase in sodium concentration (19 mmol/l in three hours), which kept the effective serum osmolality more or less equal (292 mosm/kg and 294 mosm/kg).[1] However, the treating physician was anxious about the fast decrease of glucose and rapid increase of sodium. The

Table 1. *Laboratory results*

Laboratory results	
Haemoglobin	9.1 mmol/l
Thrombocytes	381 x 10^9/l
Leukocytes	23.3 x 10^9/l
CRP	5 mg/l
Glucose	72.3 mmol/l
Sodium	103 mmol/l
Potassium	7.4 mmol/l
Chloride	69 mmol/l
Lactate	4.5 mmol/l
Creatinine	261 µmol/l
Albumin	32 g/l
Anion gap	32 mmol/l
Arterial blood gas analysis	
pH	6.90
pCO_2	12 mmHg
pO_2	70 mmHg
HCO_3^-	2.4 mmol/l
Base excess	-28.5 mmol/l
O_2 saturation	87%
Urine	
Ketones	+++

Figure 1. *Glucose concentration and effective serum osmolality. Effective osmolality = 2 x [sodium + potassium] + [glucose]*



isotonic fluids were changed to hypotonic fluids. After 18 hours the effective serum osmolality had dropped to 270 mosm/kg. Was this reflex appropriate? Before we try to answer the main topics of discussion as formulated in the introduction, we will first provide some pathophysiological background on the osmotic shifts of severe DKA that occur before and during treatment.

Pathophysiology osmotic shifts

Osmoles and the blood

Osmolality is defined as the number of moles of a compound that contribute to the osmotic pressure of a solution. Osmolality in serum is predominantly determined by electrolytes (Na^+, K^+ and Cl^-), urea and glucose. A difference in osmolality on both sides of a membrane will cause a shift of water until an equilibrium has been reached. If an osmole can cross the membrane freely, a change in its concentration will not cause a shift of water. It is not an 'effective' osmole, such as for example urea and, in the presence of insulin, glucose. The uptake of glucose in the cells is facilitated by insulin dependent glucose transporters (GLUT 4). However, in the absence of insulin this becomes impossible, and glucose will be an effective osmole. Therefore, in the presence of hyperglycaemia, due to osmosis, water will leave the cell, resulting in intracellular dehydration. Extracellularly, the – relative – water excess will decrease the sodium concentration. In healthy subjects, for every 2.5 mmol/l rise in serum glucose concentration, the serum sodium concentration will decrease by 1 mmol/l.[2]

Glucose and the brain

In the brain, glucose will first have to pass the blood-brain barrier. This transport takes place by facilitated diffusion. GLUT 1 receptors at the endothelial surface facilitate this transport, independent of insulin.[3] However, this transport is not at all complete and is not very fast. In animal studies and the scarce human studies, up until a serum glucose of 30 mmol/l, the relationship between serum and cerebrospinal fluid (CSF) glucose concentrations is linear, the concentration in the CSF being roughly 1/3 of the serum concentration, reaching a nadir of 0 mmol/l when serum glucose is 2.2 mmol/l.[4] Above a serum glucose of 30 mmol/l, some data suggest even less efficient transport of glucose.[3]

Next, glucose has to enter the brain cell facilitated by GLUT 3 receptors. It is not entirely clear whether this transport is limited as well. The glucose gradient at the blood-brain barrier, however, is most important, and causes a shift of water from the CSF to the intravascular compartment during hyperglycaemia.

In animal experiments, brain water decreased during acute hyperglycaemia, with an increase in brain sodium concentration.[5] As in hypernatraemia, cerebral cell shrinking stimulates the formation of osmolytes such as glutamine, glutamate and inositol. The concomitant increase in intracellular osmolality attracts water, resulting in restoration of cellular volume.

The brain during correction of hyperglycaemia

When therapy is initiated with volume resuscitation and insulin, glucose concentration in serum will decrease rapidly. Together with water, glucose enters the cell, resulting in an increase of the serum sodium concentration. When, due to volume repletion, diuresis ensues, this will initially lead to a loss of mostly glucose and water, thereby lowering the serum glucose and increasing serum sodium concentration.

Altogether, serum osmolality will decrease gradually. However, the brain is lagging behind. Animal models show that CSF glucose concentration decreases at a lower rate than serum glucose concentration.[6] Due to the large number of intracellular osmolytes, the brain will be relatively hyperosmolar, leading to a water shift. In animal models of hyperglycaemia, treatment with insulin and hypotonic saline increases the amount of brain water by 8%.[5]

In conclusion, time is the crucial factor. Hyperglycaemia develops gradually. The brain adapts and the reduction of brain water will be minimal. Correction of hyperglycaemia usually occurs very quickly. When this is not opposed by an increase in serum sodium, a substantial increase of brain water will follow, eventually resulting in cerebral oedema.

Additional predisposing factors of cerebral oedema in DKA

Although the osmotic shifts during treatment appear to play a crucial role in the development of cerebral oedema, the exact underlying mechanism remains unclear.

An increasing amount of evidence suggests a multifactorial pathogenesis. In some patients with hyperglycaemia (of DKA), cerebral oedema is already present at admission, so factors unrelated to treatment are relevant as well.[7]

- *Vasogenic factors*
  DKA can lead to cerebral ischaemia. Severe volume depletion and hypocapnia (respiratory compensation for metabolic acidosis) may lead to vasoconstriction resulting in cerebral hypoperfusion and possibly cytotoxic oedema.[8,9] Volume resuscitation will lead to reperfusion of the ischaemic brain. Loss of autoregulation can cause hyperaemia and vasogenic oedema.[8-10]
- *Increased permeability of the blood-brain barrier*
  The permeability of the vascular endothelium increases due to a combination of hyperglycaemia (osmotic disruption), ketoacids, cerebral hypoxia and inflammation.[3] The blood-brain barrier will be less restrictive for insulin, sodium and water.[3,5] This will accelerate the development of cerebral oedema.
- *Acidaemia*
  Initially, there is an intracellular as well as an extracellular acidosis in DKA. Organic ketoacids acidify the cytosol, activating the Na+/H+ exchanger. Treatment with insulin will (relatively) alkalise the extracellular fluid and cause hyperstimulation of the Na+/H+ exchanger. The intracellular H+ ions will be exchanged for Na+, with intracellular accumulation of Na+ and H_2O and the development of oedema.[3] Animal studies support the role of insulin in the development of cerebral oedema. Both in rats[11] and rabbits[12] treatment of hyperglycaemia without insulin did not result in cerebral oedema. However, correction of hyperglycaemia with (high) dose insulin did lead to cerebral oedema. Especially early administration of insulin, when the blood-brain barrier is less restrictive for insulin, can cause a substantial effect.[7]
  Suppletion of bicarbonate during treatment of DKA will buffer the extracellular protons. This will stimulate the Na+/H+ exchanger even more and may therefore increase the formation of oedema.[3]

Treatment of DKA

Most knowledge regarding the development of cerebral oedema in DKA is based on small, retrospective paediatric studies. Cerebral oedema predominantly occurs in children and adolescents with an incidence 7 per 1000 episodes of DKA.[3] Cerebral oedema in adults with DKA is infrequently reported, although underreporting may be substantial.[13] Due to its infrequent occurrence, guidelines for the treatment of DKA in adults do not elaborate on the prevention of cerebral oedema. However, cerebral oedema is an insidious complication and when it does occur, its course can be disastrous with rapid clinical deterioration and a high mortality. Recently, a fatal case of cerebral oedema due to DKA in an adult patient was described in this journal.[14] Moreover, adolescents are regularly admitted to the ICU with severe DKA, due to irregular lifestyle and incompliance with therapy.

Furthermore, cerebral oedema may also present with subtle signs, such as memory disturbances, and may escape attention, therefore called 'subclinical'.[15] In more than half of the children with DKA subclinical oedema was present on MRI.[16] In adults this has not been properly investigated, although reversible subclinical cerebral dysfunction with sensory evoked potentials in the first hours of treatment has been demonstrated. [17]

Optimal rate of glucose and sodium correction and main parameter to guide therapy

The main parameter to guide therapy is effective serum osmolality. A fast decrease in serum glucose is acceptable as long as the effective serum osmolality remains more or less equal. As stated earlier, glucose correction in the brain lags behind as compared with the blood. When hyperglycaemia is corrected quickly with volume

resuscitation, insulin and restoration of diuresis, the brain will become relatively hyperosmolar. The sodium concentration will have to rise, otherwise cerebral oedema will develop.

Based on this pathophysiological view, the new Dutch paediatric guideline for DKA recommends to keep effective serum osmolality constant during the first 12-18 hours of treatment.[18] This advice is also based on a retrospective study which showed that in children who developed cerebral oedema, effective serum osmolality had decreased 9 mosmol/kg (or more) during the first four hours of treatment. In children without cerebral oedema, effective serum osmolality had hardly changed during the first hours of treatment.[19]

In the recently revised guideline for DKA in adults, a rather high correction rate of serum effective osmolality (<4 mosm/kg/h) is accepted. However, in the patient described in this journal, effective serum osmolality had decreased 22 mmol within five hours.[14] This is quite near the margins of the revised guideline. There is no proven benefit of very fast correction of the hypertonic state, therefore the guideline for adults could be more stringent regarding this issue.

How to avoid a fast decrease in effective serum osmolality? First, continuous low-dose administration of insulin is sufficient to stop production of ketoacids. There are no studies which demonstrate beneficial effects of administration of insulin as a bolus.[20] Normalisation of the serum glucose concentration has no priority. Potential dangers of a sudden high insulin level are a very quick decrease in glucose concentration, as well as stimulation of the Na+/H+ exchanger, both augmenting the risk of cerebral oedema.

Second, the infusion rate can be reduced. Although manifest haemodynamic instability rectifies the use of large volumes of infusate, it occurs infrequently in severe DKA. Therefore, frequently there is no need to use these large quantities of infusate.

Third, preferably isotonic fluids should be given. A rise in the serum sodium concentration is a sine qua non for maintaining a stable blood osmolality.

Physicians have been educated that increases of more than 8-10 mmol/24 hours are dangerous due to the risk of central pontine demyelination. However, this applies for *hypotonic* hyponatriaemia with a fast increase in effective serum osmolality. In DKA with hyperglycaemia and *hypertonic* hyponatraemia, the increase in sodium will only prevent a fast decrease of the effective serum osmolality. Therefore, this should not be a reason to switch to hypotonic fluids and a rise in serum sodium of more than 8 mmol/24 hours should be accepted.

CONCLUSIONS

Hyperglycaemia develops gradually with adaptation of the brain, and should be corrected slowly because the brain lags behind (natura non facit saltus). The main parameter to guide therapy is effective serum osmolality, which should be kept well within the margins defined in the revised Dutch guideline (<<4 mOsmol/kg/hour) but by preference remain equal during the first hours. Fast reduction of serum glucose is not dangerous as long as it is compensated by an opposite trend in serum sodium concentration. However, a bolus of insulin should be avoided since it may accelerate the development of cerebral oedema. Continuous insulin administration is sufficient to stop ketogenesis. The fast rise of serum sodium concentration during correction of hyperglycaemia (*hypertonic* hyponatriaemia) is a 'sine qua non' and not a reason to switch to hypotonic fluids, since (contrary to correction of *hypotonic* hyponatriaemia) effective serum osmolality does not increase.

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