УЧЕБНО-МЕТОДИЧЕСКИЕ РЕКОМЕНДАЦИИ

Обобщающие уроки клинической патофизиологии

СИСТЕМНЫЙ ПОДХОД К ЕСТЕСТВЕНЫМ ПУТЯМ И ВЗАИМОСВЯЗАННЫМ ЗВЕНЬЯМ ПАТОГЕНЕЗА — НАРУШЕНИЯ ВОДНО-ЭЛЕКТРОЛИТНОГО ОБМЕНА. ЧАСТЬ I

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Integrative Lessons in Clinical Pathophysiology

SYSTEMIC APPROACH TO NATURAL PATHWAYS AND NETWORKING OF ETIOPATHOGENESIS — DISORDERS OF FLUIDS AND ELECTROLYTES. PART ONE

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Резюме. В этом выпуске мы начинаем серию клинических ситуационных задач по патофизиологии для самостоятельных занятий, которые будут представлены в виде тематических разборов выписок из историй болезни, требующих активного участия читателей. Каждый раз будут представлены решения задач для самоконтроля правильных ответов. Будет использоваться два метода: алгоритмический разбор задачи и метод этиопатогенетических кластеров. Задачи взяты из коллекции клинико-патофизиологических разборов кафедры патофизиологии Загребского университета, насчитывающей 1165 научно обработанных историй болезни. В этом выпуске мы начинаем с двух примеров первого типа решения проблем. (*Правильные ответы на упражнения A, B и C будут опубликованы в следующем номере журнала*).

Ключевые слова: клиническая патофизиология, этиопатогенетические кластеры, алгоритмический подход, проблемно-ориентированное обучение, осмотическое давление, водно-солевой обмен, несахарный диабет, полиурия.

Abstract. In this issue we start with the series of self-elaborative problems, which will be presented in the form of study case, imposing an active readers' participation. Each time the solutions of the tasks will be provided for a self-control of correct answers. Two methods of elaboration will be used, the algorhythimic workout of the problem and the etiopathogenetic clustering. In this issue we start with two examples of the first type of problem solver. (*Correct answers of exercise A, B and C will be published in next issue of the journal*).

Keywords: clinical Pathophysiology, etiopathogenetic clusters, algorhythmic workout, problem based learning, osmotic pressure, water and salt metabolism, diabetes insipidus, polyuria

ALGORHYTHMIC WORKOUT OF CLINICAL PROBLEM.
Pathophysiology of the diabetes insipidus [1]

In order to workout this problem, study pages 393–4, 400–1, 511–2, 516–7 and 1414–15 of the S. Gamulin, M. Marušić, Z. Kovač (Editors) Pathophysiology, Basic Mechanisms of disease — Textbook. Medicinska Naklada Zagreb, 2014.

(This problem was based on data from: Robertson GL et al. The osmoregulation of vasopressin. Kidney Internat 1976: 10: 25–37).

Diabetes insipidus syndrome manifests with polyuria, polydipsia, hypernatremia, plasma hyperosmolality as well as dehydration of the organism. The most severe cases develop circulatory shock due to hemodynamic dysfunction.

Pathogenesis of the diabetes insipidus syndrome can be divided into two dysfunction groups, pituitary (neurogenic) and nephrogenic disease. Fig. 1A shows correlation between antidiuretic hormone (ADH) concentration and urine osmolality in these two groups as well as physiological relationship of these indicators in healthy subjects. Fig. 1B indicates increased urine osmolality effect on the vasopressin secretion in these conditions.

Fig. 2 shows the effect of vasopressin on plasma osmolality in the course of pituitary diabetes treatment.

Exercise A: Repetitions of relevant knowledge (Circle one or more correct answers)

1. **Pathogenesis of the diabetes insipidus includes following mechanisms:**

a) Term root «*diabetes insipidus*» meaning «wasted flow» originates from symptoms of severe polydipsia and polyuria, whilst urine is not sweat; and these symptoms originate from impaired water balance within the organism.

b) Low urine osmolality in diabetes insipidus is a consequence of osmotic diuresis that excretes osmotic particles from peritubular compartments.

c) Decreased water permeability in collecting and distal tubules results with voided urine osmolality that equals primary urine osmolality of approximately 50–200 mOsm/kg (compare Fig. 1B).

d) Dehydration of the organism due to extracellular water loss causes plasma hyperosmolality combined with urine hypoosmolality; with insufficient water substitution and concomitant salt loss (e.g. by sweating), symptoms of hypovolemia and circulatory shock tendency clinically appear.

e) «Pure» water loss causes water shift from intracellular into extracellular space which causes cellular hypohydration and intracellular osmolality increase along with increased endogenous osmolite production.

2. Pathogenetic differences between the pituitary (hypophyseal, neurogenic) and nephrogenic diabetes insipidus, comprise the following mechanisms:

a) In nephrogenic form of the disease, due to non-functional ADH receptor and/or collecting and distal tubule cells, nephron response to otherwise elevated plasma hormone concentration is decreased (compare Fig. 1A).

b) The main pathogenetic dysfunction in nephrogenic type of the disease is excessive amount of primary urine production (fluid in the lumen at transition from Henle's loop to the distal tubule).

c) Regardless of plasma hyperosmolality in the pituitary diabetes insipidus concentration of plasma ADH does not increase, whereas nephrogenic type of the disease has high concentration of that hormone in plasma (see Fig. 1A).

d) Hypervasopressinemia with low urin osmolality (<200 mOsm/kg, see Fig.1B) and polyuria are the main features of nephrogenic diabetes insipidus, with increased ADH release from neurohypophysis activated by extracellular hyperosmolality.

e) Both forms of the disease, regardless of different molecular pathogenesis, have absent urin concentration by water reabsorption in collecting and distal tubules in common, which causes low urin specific gravity (<1,007 g/L), urine hypoosmolality, polyuria and hypernatremia.

3. For the water balance regulation and mechanisms of urin concentration, following statements are correct:

a) After the filtration, ADH reaches collecting and distal tubules where it binds to V_2-receptors on the luminal cell surface

[1] Taken from the book Z. Kovač, S. Gamulin (Ed.) Pathophysiology. Study Guide Algorhythms — Problem Solver. Book Two. Medicinska Naklada Zagreb, 2013, pg 111–5 with the consent of the Publisher and the author.

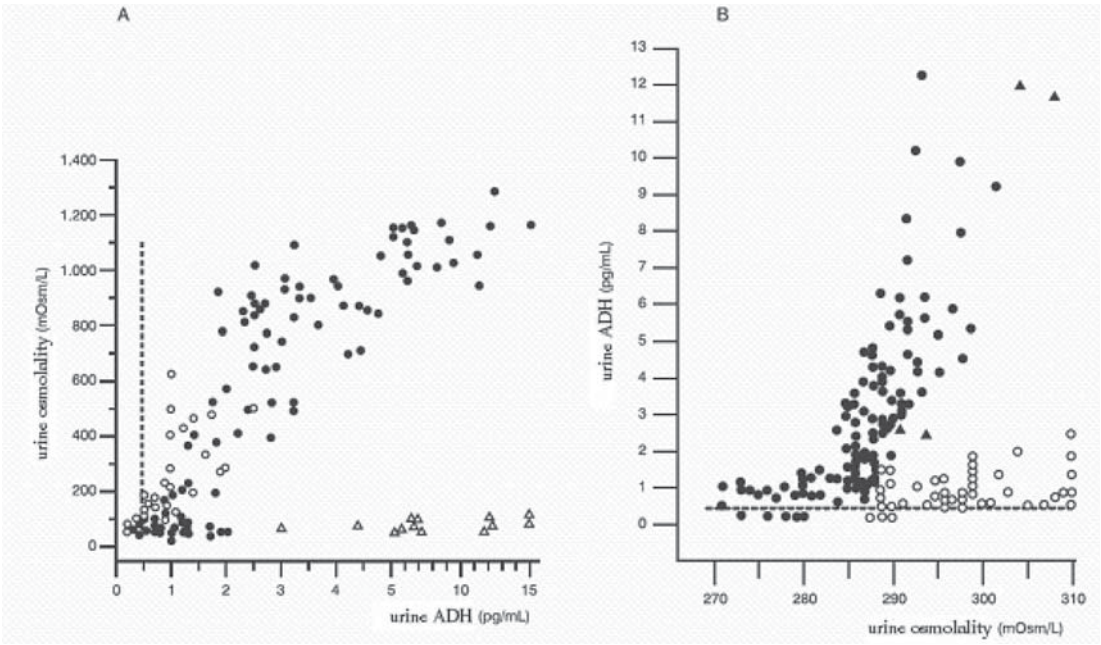

Fig. 1. Regulation of ADH secretion and urine osmolality in healthy individuals and patients with diabetes insipidus: A — relation between plasma concentration of ADH and urine osmolality; B — relation between plasma osmolality and ADH concentration in plasma. Symbol of black circle represents a healthy subject, white circle — a case of central diabetes insipidus, black or white triangles — cases of nephrogenic diabetes insipidus

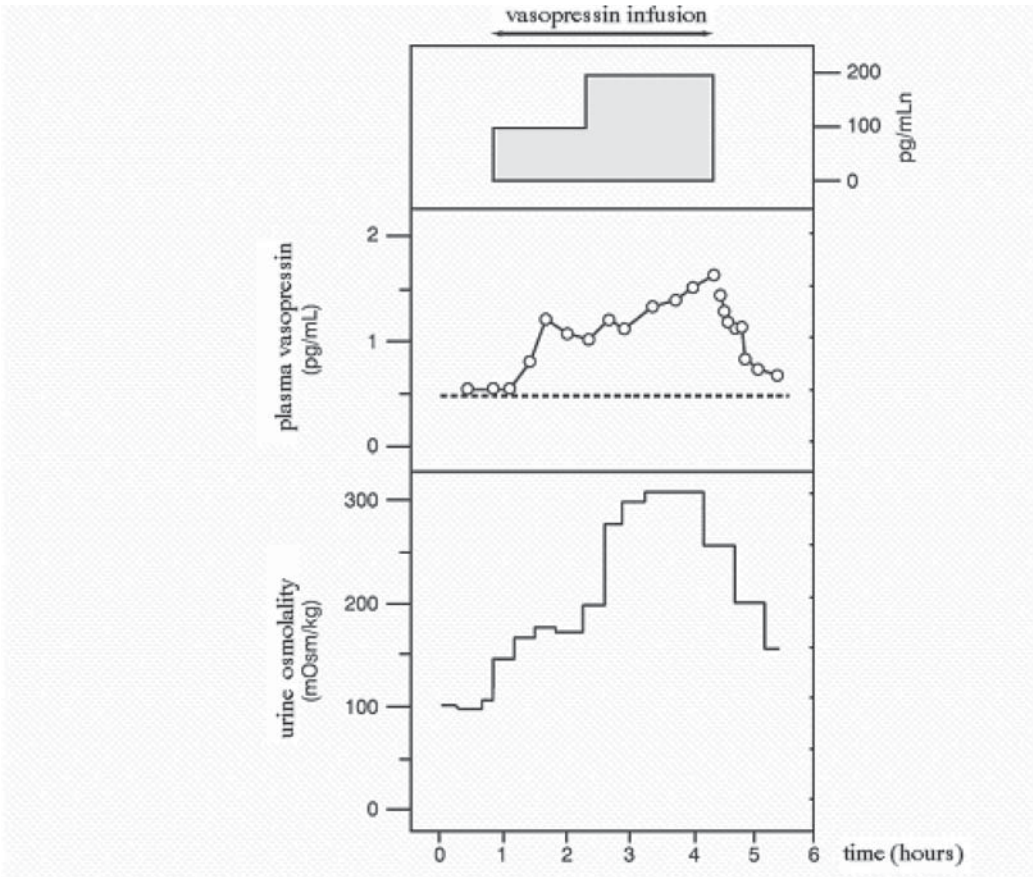

Fig. 2. Urine osmolality changes during therapeutic vasopressin infusion in central diabetes insipidus. Dashed line represents test sensitivity limits

and causes water channels on a single-layer epithelium to open.

b) Diuretic effect of the ethanol is achieved by inhibition of ADH release from the neurohypophysis, which manifests as increased urination of the hypoosmolal urine.

c) Osmolality increase above 292 mOsm/kg induces thirst sensation and polydipsia; in case of consciousness impairment (e.g. coma and sopor) water intake is absent, which accelerates hypovolemic circulatory shock development.

d) Increased plasma osmolality (approximately > 281 mOsm/kg, compare Figure 1A) physiologically causes exocytosis of pre-synthesized hormone vasopressin from the neurohypophysis.

e) Carotid and aortic baroreceptors during arterial pressure decrease, can intensely activate ADH secretion and achieve the concentration of > 1,000 mU/kg, which is ten times more powerful mechanism than the hyperosmolal activation.

4. **Etiopathogenesis of the diabetes insipidus is accurately described by the following claims:**

a) Pituitary diabetes insipidus can occur as a consequence of neoplastic growth (craniopharyngioma, pinealoma, metastatic tumors), surgical trauma of the hypothalamic region and *sella turcica*, mechanical head trauma as well as vascular lesions.

b) Common symptoms of diabetes insipidus and diabetes mellitus are based on similar pathogenesis, and include polydipsia, polyuria, plasma hyperosmolality, anion gap increase as well as extracellular space dehydration.

c) Due to dehydration of the organism in the course of diabetes insipidus, clinical features can comprise disregulatory fever, weakness and psychological alterations.

d) Hypernatremia (sometimes up to 175 mmol/L) can occur due to secondary hyperaldosteronism as well, initiated by extracellular space dehydration.

e) Patients complain of polyuria that can reach a volume of 5 to 24 L/24 hours; with frequent urination throughout the night and day for every 30 to 60 minutes.

5. Regulation of water contents within the organism, includes following pathogenetic mechanisms:

a) During profuse sweating while working in warm and humid environment, isotonic fluid evaporates through sweat; thereby body fluid osmolality practically stays the same.

b) Chronic renal failure has decreased renal response to ADH, thereby contributing to hypernatremia, hypervolemia and hypertension.

c) In pituitary diabetes insipidus management with vasopressin (compare Figure 2), urine osmolality increase is a consequence of increased collecting and distal tubule permeability for water, which causes increased water diffusion from the primary urine into peritubular space.

d) Hypercalcemic nephropathy has calcium-induced adenylate-cyclase inhibition in renal cells, which causes absent or substantially reduced cellular response to ADH thereby causing nephrogenic diabetes insipidus pathogenesis.

e) Massive vomiting and diarrhea cause dehydration of the organism, with consequentially increased ADH secretion aiming to decrease water excretion in urine and maintain sufficient extracellular space volume.

Exercise B: Algorhythmic workout of the pathogenesis

Construct the etiopathogenetic algorhythm of the disease/disorder by using elements give below: (The algorithm has two independent entries)

1. Polyuria (5–20 L/daily) and nocturia
2. Urine osmolality 50-200 mOsm/kg
3. Extracellular space dehydration
4. Plasma hyperosmolality
5. Tachycardia
6. Baroreceptor stimulation (aortic and carotid)
7. Increased ADH secretion
8. Volume receptor stimulation
9. Supraoptic and paraventricular hypothalamic nuclei stimulation
10. Hypernatremia
11. Decreased osmosis from distal and collecting tubules into peritubular space
12. Impaired V_2-receptor function in collecting and distal nephron tubules
13. Primary urine basically unaltered becomes a secondary urine
14. Very low ADH concentration despite plasma hyperosmolality
15. Constant tubular fluid osmolality along distal and collecting tubule

16. Hypovolemia
17. Arterial hypotension and circulatory shock tendency
18. Unquenchable thirst and polydipsia
19. Hypervasopressinemia (increased antidiuretic hormone concentration)
20. Intense neurohypophyseal response to plasma hyperosmolality
21. Absence of vasopressin effect on collecting and distal tubule epithelium
22. Inability of ADH production in neurohypophysis
24. Metastatic tumor infiltration causes hypophyseal dysfunction
25. Intracellular hyperosmolality
26. Water shift from intracellular into extracellular space

Exercise C: Feedback integration of the problem (Solve the tasks in following way; Correct claim + correct claim + mutually related = a; correct claim + correct claim + mutually non-related = b; correct claim + +incorrect claim = c; incorrect claim + + correct claim = d; inorrect claim + + incorrect claim = e)

1. Almost equal osmolality of the primary and secondary urine in both pathogenetic types of diabetes insipidus occurs because of relative distal and collecting tubule impermeability for water

because

physiological vasopressin (ADH) effect on distal and collecting tubule epithelium manifests as transitory depolymerization of side intercellular bonds thereby causing increased water permeability.

a b c d e

2. Decreased urine osmolality and decreased urine specific gravity in diabetes insipidus occur in spite of plasma hyperosmolality and hypernatremia

because

«pure» water loss in that condition occurs as a consequence of peritubular fluid osmolality decrease to 1/3-1/5 of extracellular space osmolality, thereby causing urine osmolality similar to the renal medulla osmolality.

a b c d e

3. In circulatory shock development due to diabetes insipidus, two pathogenetic components can be excluded, hypovolemic and vasohypotonic, that synergistically contribute to the arteriovenous pressure difference decrease and reduced tissue perfusion

because

in water metabolism regulation within the organism, hemodynamic regulation is superior to the osmotic mechanisms, which has protective function for extracellular space volume.

a b c d e

Additional questions:

4. Calculate relationship between physiologically maximal and minimal urine concentration.

5. Calculate total osmol quantity in extracellular space during normoosmolality (280–295 mOsm/L). Quantify water loss from both extracellular and intercellular spaces during hyperosmolality measuring 310 mOsm/L, as in diabetes insipidus (compare Figure 1A).

ALGORHYTHMIC WORKOUT OF CLINICAL PROBLEM. Kinetics of body fluid adaptations during infusion of saline or glucose solution in healthy subjects [2]

In order to workout this problem, study pages 383–9, 390–3, and 1390–6 of the S. Gamulin, M. Marušić, Z. Kovač (Editors) Pathophysiology, Basic Mechanisms of disease — Textbook. Medicinska Naklada Zagreb, 2014.

(This problem was based on data from papers: Lobo D.N. et al. Dilution and redistribution effects of rapid 2-litre infusions of 0,9% (w/v) saline and 5% (w/v) dextrose on hematological parameters and serum biochemistry in normal subjects: a double blind crossover study. Clin Sci 2001; 101: 173-9; Mange K et al. Language guiding therapy: A case of dehydration versus volume depletion. Annals Intern Med 1997; 127: 848–53).

Physiological effects of isotonic fluid infusion have been investigated on healthy subjects using crossover double bind study. Five volunteers have been intravenously infused

[2] Taken from the book Z. Kovač, S. Gamulin (Ed.) Pathophysiology. Study Guide Algorhythms — Problem Solver. Book Two. Medicinska Naklada Zagreb, 2013, pg 126–31, with the consent of the Publisher and the author.

with 2L of saline solution in one hour, and the other five were given 2 liters of 5% glucose solution. Subjects were tested for alterations in body mass, hematologic parameters, serum electrolyte osmolal shifts as well as dynamics of excretion and urine properties. The experiment was repeated on subjects after 7–10 days using the other solution. All subjects remained stable throughout the experiment in duration of six hours. Figure 1 shows relative alterations in body mass, albuminemia, hemoglobinemia and hematocrit, and Figure 2 illustrates alterations in serum osmolality as well as shifts in glucose, sodium, potassium, chlorides and bicarbonates in two groups of subjects. Mean corpuscular volume of erythrocytes did not alter more than ± 1 fL (referent range 85–95 fL). Table 1 compares indicators of urodynamics, composition and osmolality of urine in two groups of subjects. All of them had glucosuria in the first urine following glucose infusion, but glucosuria was absent in pre-infusion urine and other post-infusion urine samples.

One subject has developed transient periorbital edema after infusion of both fluids, and one other after the saline solution infusion. Five subjects described transitory symptoms of insecurity approximately two hours after the glucose infusion, which correlated with a period of demonstrated reactive hypoglycemia (compare Figure 2).

Table 2 lists calculated osmolalities and volumes of body compartments in subjects infused with 1 liter of isoosmolal saline or glucose solution. The calculation describes a steady state with ignored urinary fluid losses.

Exercise A: Repetitions of relevant knowledge (Circle one or more correct answers)

1. According to data in Figures 1 and 2, for alterations in subjects in the first hour which are common to both groups, following claims are correct:

a) An increase in body mass of 2 kg directly results from fluid administration, whilst majority of infused fluid during that period located in the extracellular space, which was thereby adaptively increased.

b) Hypoalbuminemia which emerges from dilution by isotonic fluid contributes to a decrease in oncotic plasma pressure, thereby increasing capillary net filtration in the organism.

Table 1

Comparison of urodynamics, electrolyte contents and urine osmolality indicators in two groups of subjects

Indicator	Saline solution	5% glucose solution	p-value
Time of first urination (min)	212	78	0,002
Urination frequency in first 6 hours	1,7	3,4	0,002
Total volume of urine in first 6 hours (mL)	563	1663	<0,001
Total excretion of Na^+ in first 6 hours (mmol)	95	26	<0,001
Total excretion of K^+ in first 6 hours (mmol)	37	10	<0,001
Pre-infusion urine osmolality (mOsm/kg)	880	773	0,87
Post-infusion urine osmolality (mOsm/kg)	630	129	<0,001

Table 2

Characteristics of solutions and balanced fluid distribution in body compartments during infusion of one litre 5% glucose solution or 0.9% saline solution

Indicator	Saline solution	5% glucose solution
Solution properties		
Sodium contents (mmol)	145	0
Water contents (mL)	1000	1000
Alterations in body compartments		
Extracellular space increase (mL)	1000	333
Intracellular space increase (mL)	0	667
Osmolality decrease (%)	0	2.5
Plasma volume increase (mL)	250	83

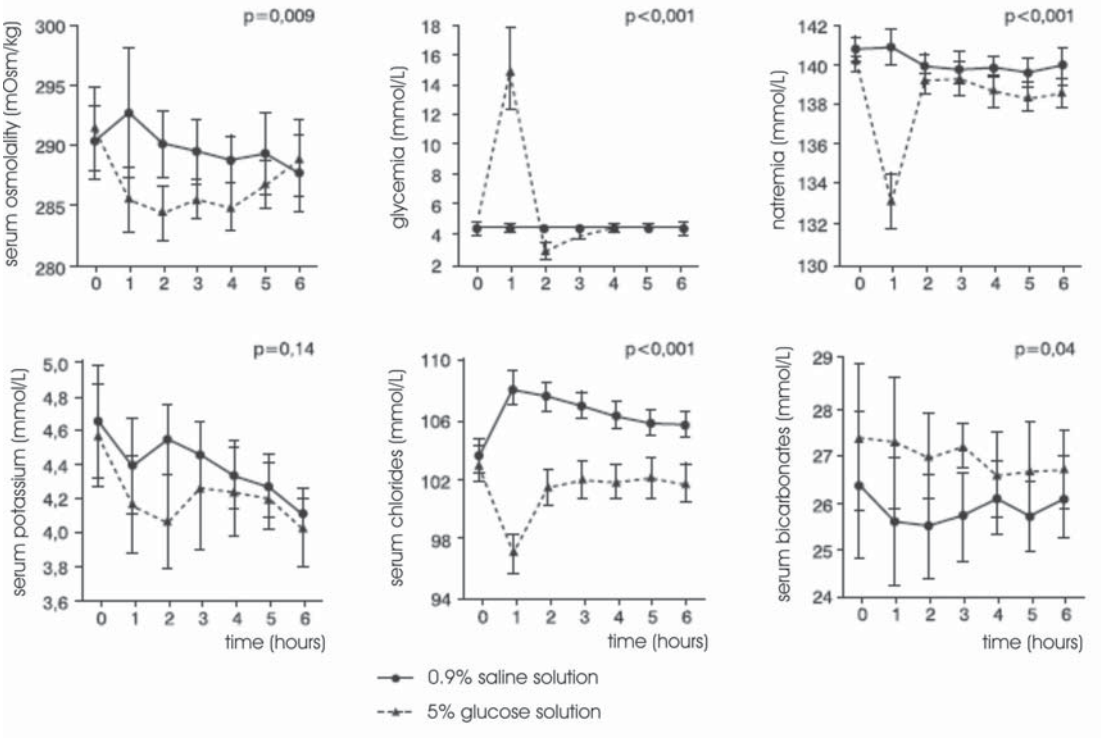

Fig. 1. Alterations in body mass, albuminemia, hemoglobinemia and hematocrit during and after infusion of saline or glucose solution. 2L of isoosmolal fluids has been intravenously administered to subjects in 0–1 hour period

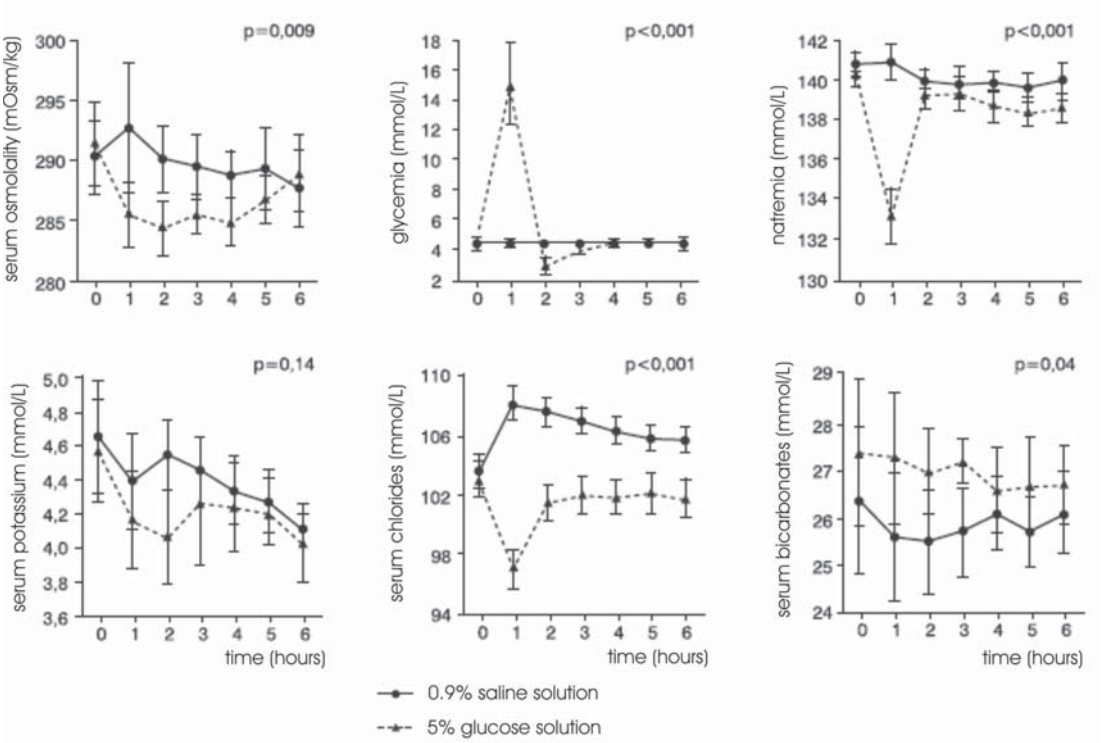

Fig. 2. Dynamics of changes in osmolality of plasma, glycemia and concentration of electrolytes in plasma in subjects treated as described in Figure 1

c) A relative decrease in hemoglobin concentration in blood is smaller in relation to a relative decrease in albuminemia, since hemoglobin values include corpuscular volume of blood in addition to plasma in measurement and calculation procedures.

d) Serum potassium concentration only insignificantly decreases, since approximately 30-times more of that electrolyte is located in the extracellular space in relation to the intracellular space in the body.

e) Hematocrit decrement for about 7% in both groups of subjects occurs due to increased volume of plasma; that plasma volume increase is relatively smaller, since volume of plasma normally exceeds volume of cells in blood.

2. According to data in Figures 1 and 2, differences between two tested groups are accurately described by the following claims:

a) Hyperglycemia, which appears only in the group with isotonic glucose infusion, occurs in the healthy organism as a result of intensely stimulated gluconeogenesis and glycogenolysis.

b) As opposed to infusion of 5% glucose, during saline solution infusion body mass of subjects does not return to the initial value in first seven hours of experiment due to slower excretion of fluid from the organism.

c) Hyponatremia and hypochloremia in the first hour of 5% glucose infusion are interpreted by dilution effect on these electrolytes, not present during saline solution infusion which contains them in its composition.

d) Although subjects have been administered isoosmolal solutions, entry of infused glucose in the intracellular space and its metabolism in plasma produce hypoosmolality, which is not encountered during infusion of saline solution.

e) Despite serum alterations in concentrations of electrolytes and glucose as well as plasma osmolality in subjects with intravenously administered glucose solution (not encountered during infusion of saline solution), erythrocyte mean corpuscular volume does not change, which is interpreted by erythrocyte membrane permeability for glucose.

3. Redistribution of body fluids and dynamics of urinary excretion during infusion of isoosmolal fluids according to data in Tables 1 and 2 are correctly described by the following claims:

a) Oncotic pressure of plasma proteins is a main force that counteracts filtration on the capillary wall; during isoosmolal fluid infusion (as in subjects) partial decrement of oncotic pressure directly participates in fluid redistribution between extracellular and intracellular compartments.

b) Although 5% glucose solution is isoosmolal, an excess of «pure» water in relation to osmolutes forms during infusion due to rapid glucose metabolism, thereby producing hypoosmolality of the extracellular space.

c) During infusion of glucose solution, in distinction from infusion of saline solution, beside pressure and volume receptors, osmotic receptors are being stimulated as well, thereby significantly accelerating and enhancing dynamics of fluid excretion from the organism.

d) An increase in volume of plasma despite decrement in oncotic pressure results from isoosmolal hyperhydration which reestablishes a new balance of Starling's forces on the capillaries.

e) Transitory glucosuria in healthy subjects following glucose infusion results from excessive renal load, when filtration of glucose exceeds the reabsorption maximum and is being washed away into the urine.

4. Mechanisms underlying symptoms and signs of anisoosmolality and hydration disorders are accurately described by the following statements:

a) Hypovolemia and hypohydration cause tachycardia and decreased central venous pressure, and can lead to orthostatic hypotension and positive Schellong's test.

b) Peripheral edemas, hemodynamic according to the mechanism of origin, develop during right heart decompensation and are augmented by concomitant retention of isoosmolal fluid due to simultaneously increased secretion of ADH.

c) In hyperosmolal disorders, dehydration and cell shrinkage cause central nervous system dysfunctions (irritability, epilepsy) with increased production of endogenous osmolutes intracellularly.

d) Hypohydration and hypovolemia initiate endocrine adaptive response which comprises hyperaldosteronemia, hypervasopressinemia and hypercatecholaminemia which

cause compensatory retention of salt and water as well as hemodynamic adaptations.

e) Extracellular fluid hyperosmolality stimulates ADH regulation, stimulates sensation of thirst and water consumption (polydipsia), can cause a reduction in mean corpuscular volume and lead to anorexia, nausea and vomiting.

5. Etiopathogenetic role of osmolality and hydration disorders in the organism is accurately described by the following claims:

a) Hypoosmolal disorders can result from primary positive water balance and primary negative sodium balance, accompanied by alterations in size and osmolality of the intracellular space in hyperhydration as well as hypohydration.

b) Hypoosmolal hypohydration can develop during administration of 5% glucose solution (as in subjects from the assignment) since glucose enters cells by facilitated diffusion where it leads to hyperosmolality.

c) Hyperhydration-related isoosmolal conditions cause comparable increase of interstitial volume and volume of plasma, while intracellular space volume remains constant.

d) Hypohydration in diabetes insipidus occurs due to primarily negative water balance (loss of «pure» water); hyperosmolality develops in the extracellular space and stimulates sensation of thirst.

e) Hypohydration and hypovolemia develop in adrenal insufficiency; transitory increase in intracellular compartment can occur due to hypoosmolality of the extracellular space.

Exercise B: Algorhythmic workout of the pathogenesis

Construct the etiopathogenetic algorhythm of the disease/disorder by using elements give below:

1. Hypoglycemia (transitory)
2. Infusion of 2L of 5% glucose solution
3. Plasma osmolality decrease for approximately 10 mOsm/L
4. Decrease in plasma concentration of sodium ions in the first hour following the infusion
5. Decreased fluid reabsorption in distal and collecting renal tubuli
6. Stimulation of volume receptors
7. Repression of osmotic receptors
8. Decreased urine osmolality to approximately on sixth of the pre-infusion value
9. Stimulation of pressure receptors
10. An increase in body mass for 2 kg in one hour (see Figure 1)
11. Reduced oncotic pressure
12. Hypoalbuminemia
13. Decreased hematocrit
14. Stimulated insulin secretion
15. Transient hyponatremia and hypochloremia
16. Transport maximum overflow for renal reabsorption of glucose
17. Transient hyperglycemia
18. Increased storage and utilization of glucose in cells
19. Accelerated diuresis and increased volume of urine
20, Increased volume of plasma and intercellular space
21. Hypohemoglobinemia
22. Transient glucosuria
23. Decreased osmolality of urine
24. Initiated mechanisms of osmotic diuresis
25. Decreased secretion of ADH in neurohypophysis
26. Hyperhydration of the organism

Exercise C: Feedback integration of the problem (Solve the tasks in following way; Correct claim + correct claim + mutually related = a; correct claim + correct claim + mutually non-related = b; correct claim + incorrect claim = c; incorrect claim + correct claim = d; inorrect claim + incorrect claim = e)

1. Water entered by infusion of 2L 5% glucose solution represents organismic load by «pure water», which is being rapidly excreted from the organism after correction of hyperglycemia through the mechanism of osmotic diuresis (compare claims 3a and 3b)

because

three times larger volume of urine excreted during initial six hours in comparison to the group receiving infusion of saline solution results from increased resorption of osmolutes in distal and collecting nephron tubuli under the influence of antidiuretic hormone.

a b c d e

2. Hypoalbuminemic and hypohemoglobinemic effect and decreased hematocrit last

significantly longer in subjects with infused saline solution (see Figure 2)

because

these subjects excrete urine with approximately comparable osmolality as in preinfusion time (see Table 1), which indicates afunctional mechanism of urine concentration/dilution.

a b c d e

3. Infusion of saline solution causes isoosmolal hyperhydration in subjects, whereas infusion of glucose solution causes hypoosmolal hyperhydration

because

hypoosmolal hyperhydration is characterized by net influx of water intracellularly and an increase in intracellular volume; there is no change in intracellular volume in isoosmolal hyperhydration (compare Table 2).

a b c d e

Additional questions

4. Calculate the difference between osmolalities of saline solution (0.9% NaCl solution) and 5% glucose solution. Relative molar mass of glucose is 180, Na^+ 23 and Cl^- 35 daltons.

5. How much did the contents of kitchen salt in the extracellular space increase relatively, during 1 hour, on abscises of curves 1 and 2 during infusion of saline or glucose solution, under assumption of minimal exchange with the intracellular space during that period. Extracellular space volume is 15L, Na^+ concentration is 140 mmol/L and Cl^- 100 mmol/L.