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THE INFLUENCE OF XYLATE ON THE VOLUMO- AND OSMOREGULATORY FUNCTION OF THE KIDNEYS IN DIABETES COMPLICATED BY THE SYNDROME OF ENDOGENOUS INTOXICATION OF PURULENT-SEPTIC ORIGIN

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Key words: *volume and osmoregulatory function of the kidneys, insulin-independent diabetes mellitus, syndrome of endogenous intoxication of purulent-septic origin, xylate*

Ключові слова: *об'ємна й осморегуляторна функція нирок, інсулінонезалежний цукровий діабет, синдром ендогенної інтоксикації гнійно-септичного походження, ксиліт*

Ключевые слова: *объемная и осморегуляторная функция почек, инсулиннезависимый сахарный диабет, синдром эндогенной интоксикации гнойно-септического происхождения, ксилит*

Abstract. *The influence of xylate on the volumo- and osmoregulatory function of the kidneys in diabetes complicated by the syndrome of endogenous intoxication of purulent-septic origin. Konovchuk V.M., Kushnir S.V., Andrushchak A.V., Andrushchak M.O. The combination of insulin-independent diabetes mellitus with endogenous purulent-septic genesis syndrome is a fairly common nosology. The search for ways to optimize the results of its treatment, after screening observations, led to the expediency to consider the pharmacodynamic aspects of the*

action of polyhydric alcohols through the prism of homeostatic support functions. Detailing this direction was focused on the consideration of the action of xylate mediated through the volumetric and osmoregulatory function of the kidneys. The effect of xylate on the volumo- and osmoregulatory function of the kidneys in insulin-independent diabetes mellitus complicated by the syndrome of endogenous intoxication of purulent-septic origin was investigated. The study group consisted of 53 patients with insulin-independent diabetes mellitus complicated by the syndrome of endogenous intoxication of purulent-septic origin (IDCSEI). Under the condition of infusion loading (3 ml/kg/h for three hours) with Ringer's solution or xylate within the fragments of planned intensive care, indicators characterizing the state of the volumo- and osmoregulatory function of the kidneys were investigated. The loading with Ringer's solution in patients with IDCSEI increases sodium clearance by $260 \pm 47.8\%$ (Δ , $p=0.020$), without changing the concentration of sodium ions in the blood plasma and filtration fraction and purifying the blood plasma from osmotically active substances $147 \pm 46.9\%$ (Δ , $p=0.011$). Extension of the extracellular space by infusion solutions by 3 ml/kg/h for three hours in patients with insulin-dependent diabetes mellitus, complicated by the syndrome of endogenous intoxication by purulent-septic genesis, activates volumetric and osmoregulatory function. Extension of extracellular space with infusion solution by 3 ml/kg/h for three hours in patients with insulin-independent diabetes mellitus activates volumo- and osmoregulatory function. Activation of volumetric function occurs by reducing the reabsorption of sodium and water in the proximal nephron, without increase of glomerular filtration rate, increasing the distal transport of sodium and water.

Реферат. Вплив ксилату на волюмо- та осморегуляторну функцію нирок при цукровому діабеті, ускладненому синдромом ендогенної інтоксикації гнійно-септичного генезу. Коновчук В.М., Кушнір С.В., Андрущак А.В., Андрущак М.О. *Поєднання інсулінонезалежного цукрового діабету із синдромом ендогенної інтоксикації гнійно-септичного генезу є достатньо розповсюдженою нозологією. Пошуки шляхів оптимізації результатів її лікування, після скринінгових спостережень, привели до доцільності розглянути фармакодинамічні аспекти дії багатоатомних спиртів через призму гомеостатичних функцій забезпечення. Деталізація цього напрямку була зосереджена на розгляді дії ксилату, опосередкованої через волюмо- та осморегуляторну функцію нирок. Досліджено вплив ксилату на волюмо- та осморегуляторну функцію нирок при інсулінонезалежному цукровому діабеті, ускладненому синдромом ендогенної інтоксикації гнійно-септичного генезу. Досліджувану групу склали 53 пацієнти з інсулінонезалежним цукровим діабетом, ускладненим синдромом ендогенної інтоксикації гнійно-септичного генезу (ІНЦДСЕІ). За умови інфузійного навантаження (3 мл/кг/год протягом трьох годин) розчином Рінгера або ксилату в межах фрагментів планової інтенсивної терапії досліджували показники, що характеризують стан волюмо- та осморегуляторної функції нирок. Навантаження розчином Рінгера пацієнтів з ІНЦДСЕІ збільшує кліренс натрію на $260 \pm 47,8\%$ (Δ , $p=0,020$), без зміни концентрації іонів натрію в плазмі крові та фільтраційної фракції та очищення плазми крові від осмотично активних речовин $147 \pm 46,9\%$ (Δ , $p=0,011$). Розширення позаклітинного простору інфузійними розчинами на 3 мл/кг/год протягом трьох годин у пацієнтів з інсулінозалежним цукровим діабетом, ускладненим синдромом ендогенної інтоксикації гнійно-септичного генезу, активізує об'ємну та осморегуляторну функцію. Збільшення об'єму позаклітинного простору інфузійними розчинами в режимі 3 мл/кг/год протягом трьох годин у пацієнтів з інсулінонезалежним цукровим діабетом. Активація волюморегуляторної функції нирок проходить шляхом зменшення реабсорбції натрію та води в проксимальному відділі нефрону, без збільшення швидкості клубочкової фільтрації, підвищенням дистального транспорту натрію та води.*

The infusion therapy is basic in intensive care of disorders of biological unity of patients [4]. Its priorities are determined by the content of ingredients that are important for maintaining homeostasis and correcting its quality. Today, the combination of insulin-independent diabetes mellitus with endogenous intoxication syndrome, including purulent-septic genesis (IDSCDI), is a fairly common nosology [9]. It requires comprehensive treatment, thorough comprehensive monitoring, individualization of intensive care measures, taking into account the numerous complications of diabetes mellitus and factors of endogenous intoxication syndrome aimed at forming the spectrum of multi organ injury [7]. Therefore, clinical situations, questions, and discussions are constantly emerging regarding the choice of infusion therapy for the purpose of rehabilitation of the target organs of

diabetes combined with metabolic disorders initiated by concomitant endogenous intoxication syndrome [5, 6]. One of the answers to these questions is in the area of consideration of the action of the appropriate preparation of infusion therapy of diabetes mellitus (DM) through the prism of the volumetric and osmoregulatory function of the kidneys. This drug can be xylate, because its capabilities meet the requirements of correction of this pathology. In particular, the main component of xylate, xylitol, is a natural by-product of carbohydrate metabolism in humans and animals. Its pharmacokinetics is not associated with specific hormonal or enzymatic transport mechanisms. The degree of absorption does not depend on the age of the patient. It associates the pentose phosphate cycle with the exchange of uronic acid in its mechanism of action, and the end product of oxidation is carbon dioxide,

which is eliminated by the lungs. Compared to glucose, xylitol is a more efficient source of energy conversion and its metabolism is independent of insulin. It has lipotropic and anti-ketogenic activity. Xylitol stimulates glycogen synthesis in the liver, insulin secretion. It improves microcirculation, normalizes water-salt metabolism and acid-alkaline state, has a detoxifying effect in burn disease, protracted purulent processes and infectious diseases [5,8].

The goal of the work is to investigate the effect of xylate on the volume- and osmoregulatory function of the kidneys in insulin-independent diabetes mellitus complicated by the syndrome of endogenous intoxication of purulent-septic origin.

MATERIALS AND METHODS OF RESEARCH

The study is open, randomized, prospective and controlled. Bioethics Protocol No. 9 of 20.06.2019.

The patients with insulin-independent diabetes mellitus complicated by the syndrome of endogenous intoxication of purulent-septic origin were studied. Inclusion criteria: ICCD, age 42-65 years, established disease experience 5-12 years; from anamnesis: correction with diet, regimen, tableted hypoglycemic agents, insulin (9%); actual glycemia – 8-16 mmol/l, glycosylated hemoglobin >7%, transient microalbuminuria (30-300 mg/day); various clinical manifestations of angiopathy and neuropathy without significant disturbance of functions of the affected organs and systems were registered. The course of ICCD in these patients was complicated by the acute surgical infection after surgical repair of the lesion of different localization caused by the association of aerobic gram-positive and gram-negative flora; was accompanied by endogenous intoxication syndrome of purulent-septic genesis on the scale of cell-humoral intoxication index of 20-50 points) [2].

All patients (n=53) received appropriate surgical debridement and comprehensive standard intensive care. In-hospital sugar correction was performed with insulin at glycemia >10mmol/l. When enrolled, in the intensive care setting, the patients received Ringer's and xylate infusion solutions, and indicators characterizing the volumetric and osmoregulatory function of the kidneys were examined within the Ringer's solution infusion range and, after 20-24 hours, xylate. The group characteristics were determined: I-IV gr – ICDEI, among them – A: indicators in patients before infusion of Ringer's solution (group I) or xylate (group III); B – after infusion of Ringer's solution (group II) or xylate (group IV). The solution infusion mode is 3 ml/kg/h for three hours. The examination (urine analysis) took 4 h, taking into account the time of infusion load. The indicators of values studied in biological environments – urine, blood plasma [3] are shown in the table.

We used the Student's t-test for dependent and independent samples (Excell statistical package trial version) [1].

RESULTS AND DISCUSSION

There were two periods in terms of infusion therapy of patients with IDCSEI (n=53): the first one concerned the study of the effect of Ringer's solution (3 ml/kg/h for three hours) on the volumetric and osmoregulatory function of the kidneys, the second (after 20-24 hours) – the effects of xylate under the same conditions (table). The involvement of the kidneys in the release of extracellular space from a certain volume of fluid and osmotically active substances (UARs) as well as urination is an ongoing process. The clearance characteristics are the most informative in a metric that reflects these features. In particular, sodium clearance, characterizes the volume of protein-free fluid containing sodium at a concentration consistent with blood plasma and excreted by the kidneys. The loading with Ringer's solution in patients with INCDEI (group II) increased clearance by 1.85 ± 0.34 ml/min ($260 \pm 47.8\%$; Δ , $p=0.020$). At the same time, the concentration of sodium ions in the blood plasma, the rate of glomerular filtration and the filtration fraction of the cation remained virtually unchanged. Therefore, it should be considered that sodium clearance was formed by other components that determine the excretion of the cation, the excreted fraction of sodium and water. Further analysis indicates that the reabsorbed water fraction decreased by $1.67 \pm 0.41\%$ (Δ , $p=0.015$) and the reabsorbed sodium fraction – by $1.53 \pm 0.26\%$ (Δ , $p=0.022$). Considering that the sodium free water clearance and the reabsorption of osmotically free water increased by $35 \pm 11.7\%$ (Δ , $p=0.011$) and $147 \pm 44.5\%$ (Δ , $p=0.014$, respectively), it should be considered that the depression of the reabsorption of water and sodium ions occurred at the level of the proximal nephron, and the distal one worked in the compensatory mode.

The infusion loading of patients with IDCSEI with Ringer's solution activates purification of blood plasma from OAR) in the observation interval by 4.7 ± 1.51 ml/min ($147 \pm 46.9\%$; Δ , $p=0.011$), excreted fraction – by $3.9 \pm 1.1\%$ (Δ , $p=0.013$), and the excretion rate based on the standardized glomerular filtration rate (GFR) – by 1290 ± 416.1 mcos/min ($154 \pm 49.7\%$; Δ , $p=0.013$). At the same time, the filtration fraction of OAR did not undergo any significant changes: 35.99 ± 0.59 mcm/min – to increase the extracellular space volume by Ringer's solution; 36.84 ± 0.62 msm/min after increase in extracellular volume ($p>0.05$) and did not lead to a decrease in OAR concentration in blood plasma.

The effect of xylate on the volumo-and osmoregulatory function of the kidneys in insulin-independent diabetes mellitus complicated by the syndrome of endogenous intoxication of purulent-septic origin (M±m)

Indexes	INCDEI (n = 53)			
	I gr	II gr	III gr	IV gr
V, ml/min	1.22±0.03	3.24±0.10**	1.23±0.03	3.58±0.08* **
EF _{H₂O} , %	1.03±0.02	2.70±0.03**	1.05±0.02	2.98±0.03* **
GFR, ml/min	118.0±1.7	120.0±1.9	120.0±1.8	122.0±1.9
P _{Na} , mmol/l	140.0±1.2	139.0±1.1	141.0±1.2	138.0±1.3
P _{Na} ·GFR, mmol/min	16.5±0.21	16.7±0.24	16.9±0.23	16.7±0.25
U _{Na} , mmol/l	80.0±3.5	109.0±3.6**	79.0±3.4	110.0±3.5**
U _{Na} V, mmol/min	97.9±3.1	354.2±6.4**	98.2±3.2	393.1±6.7* **
C _{Na} , ml/min	0.71±0.03	2.55±0.04**	0.69±0.03	2.87±0.05* **
EF _{Na} , %	0.60±0.02	2.13±0.03**	0.58±0.02	2.36±0.04* **
U _{Na} V/GFR*100, mmol/min	83.0±2.9	296.0±6.1**	82.0±2.8	318.0±5.9* **
C _{Na} ^{H₂O} , ml/min	0.50±0.004	0.69±0.010**	0.54±0.004	0.72±0.011**
P _{osm} , mos/l	305.0±2.0	307.0±1.9	304.0±1.7	306.0±1.9
U _{osm} , mos/l	808.0±17.5	754.0±18.6**	801.0±18.2	742.0±19.3**
U _{osm} V, mcm / min	986.0±18.2	2443.0±41.0**	987.0±18.9	2657.0±39.7* **
C _{osm} , ml/min	3.2±0.07	7.9±0.15**	3.3±0.07	87±0.16* **
EF _{osm} , %	2.7±0.06	6.6±0.08**	2.8±0.06	7.1±0.09* **
U _{osm} V/GFR*100, msm/min	836.0±15.0	2036.0±27.3**	822.0±15.8	2178.0±31.0* **
T ^c _{H₂O} , ml/min	1.9±0.05	4.7±0.12**	2.0±0.04	5.1±0.10* **

Note: I - IV gr. - INCDEI; A - patients before infusion of Ringer's solution (group I) or xylate (group III); B - patients after infusion of Ringer's solution (group II) or xylate (group IV); * / p<0.05 - reliability of indicators between I gr. and III gr., II c. and IV gr., ** / p<0.05 - reliability of indicators between I gr. and II gr.; III gr. and IV gr.

V is diuresis,

EF_{H₂O} - excreted fraction of water,

GFR - glomerular filtration rate,

P_{Na} - the plasma concentration of sodium,

P_{Na}GFR - sodium filtration fraction,

U_{Na} - sodium concentration in urine,

U_{Na}V - excretion of sodium with urine,

C_{Na} - sodium clearance,

EF_{Na} - excreted sodium fraction,

U_{Na}V / GFR * 100 - standardized sodium excretion,

C_{Na}^{H₂O} - clearance of sodium water,

P_{osm} - the concentration of OAR in blood plasma,

U_{osm} - the concentration of OAR in the urine,

U_{osm}V - excretion of UAR with urine,

C_{osm} - OAR clearance,

EF_{osm} - excreted fraction of OAR,

U_{osm}V / GFR * 100 - standardized excretion of OAR,

T_{H₂O}^c - reabsorption of an osmotically free fluid.

The intensive care in the format of randomization included infusion and study of the action of xylate 20-24 h after the study of the action of Ringer's solution (group IV). The medicine with diuretic action were abstained in terms of the use of complex therapy. The characteristics of starting indicators (I gr, III gr) of the volume- and osmoregulatory function of the kidneys are presented in the table. Among them, no statistically significant changes are registered.

The infusion load of xylate at INCDEI (Group IV) increases the clearance of sodium ions by 2.18 ± 0.39 ml/min ($316.0 \pm 57.2\%$, Δ , $p=0.028$). Its value is due to a decrease in reabsorption of water in the kidney tubules (by $1.90 \pm 0.42\%$, Δ , $p=0.017$) and sodium ($1.78 \pm 0.31\%$, Δ , $p=0.021$), since the filtration fraction of the cation did not change. The degree of distal sodium elimination correction reflects the clearance of sodium free water (Table), and indicates that the infusion load with xylate reduces the extracellular water volume in patients with IDCSI by limiting the reabsorption of water and sodium ions in the proximal compartment. The changes in the clearance of osmotically active substances were 5.4 ± 1.73 ml/min (Δ , $p=0.010$), which corresponds to the activation of purification of blood plasma from osmotically active substances by $164 \pm 52.5\%$ (Δ , $p=0.012$), compared with the starting values, and are characterized by an increase of excreted fraction by $4.3 \pm 1.2\%$ (Δ , $p=0.014$); the occurrence of osmotic diuresis in active nephrons, which is $166 \pm 51.1\%$ (Δ , $p=0.013$) of the difference between the initial values and the final characteristics, subject to standardization of the glomerular filtration rate. The comparison of the clearance characteristics of the state of volume- and osmoregulatory function of the kidneys by the results of

their values after the increase of extracellular space (group II, group IV) shows that xylate 56% ($p<0.05$) more strongly activates the volume-regulatory function of the kidneys than Ringer's solution and, respectively, osmoregulatory – by 17% Δ , $p<0.05$). The data obtained by infusion loading solutions indicate the presence of a universal mechanism of reaction of the kidneys to increase the volume of extracellular space, for example, Ringer's solution or xylate, and subject to the design of the study determines the compensatory adaptation range of their regulatory processes, and the level of non-regulatory processes namely: glomerular filtration rate and filtration fraction of sodium ions is unchanged, proximal transport of water and sodium – suppressed, distal transport of water and sodium activates.

CONCLUSIONS

1. Extracellular space volume increase with infusion solution by 3 ml/kg/h for three hours in patients with insulin-independent diabetes mellitus complicated by endogenous purulent-septic genesis syndrome indicates that xylate is by 56% p (clearance) prevails volume regulatory activity of Ringer's solution and, accordingly, osmoregulatory – by 17% ($p<0.05$).

2. Activation of the voleregulatory function of the kidneys by infusion loads in patients with insulin-independent diabetes mellitus complicated by the syndrome of endogenous intoxication of purulent-septic genesis indicates the presence of a mechanism of reaction of the kidneys to increase the volume of extracellular space, which is determined by the level of extracellular space. Sodium is unchanged, proximal transport of water and sodium is suppressed, distal transport is activated.

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