Infusion GIK solutions

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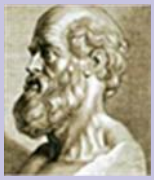
July 10, 1881 Landerer successfully performed injection of "sodium chloride physiological solution" to patient and ensured perpetuation for this infusion medium. Last century became an epoch of fluid management formation and development. This medical branch is successfully developing nowadays.

In the 90-s years of last century crystalloids were generally made in hospital pharmacies, they had limited terms of storage. At present time there is a clear trend of finished pharmaceutical forms of infusion solutions production, they are produced in pharmaceutical factories. Fluid management is an important tool for complex treatment of many diseases. Doctor must clearly know the aim of infusion solution use, the drug quantitative composition and have comprehensive information about its mechanism of action.



Sublata causa tollitur morbus
Disease resolves with elimination of cause
Hippocrates

Birth of metabolic approach to CAD treatment traditionally is associated with glucose-insulin-potassium solution (GIP). Widespread long-term GIP use is based on switch effect of inefficient free fatty acids oxidation on damaged by hypoxia myocardium towards glucose, that is more favorable in conditions of hypoxia.

Maintaining normal blood plasma potassium concentration is one of the major conditions of a rational fluid management.

Potassium is the main cation and osmotic component of intracellular fluid. Health adults have only 2% (60-80 mEq/L) of total body potassium (3000-4000 mEq/kg of body weight) in extracellular fluid [1]:

• K^+ cell concentration is about 160 mmol/L, i. e. is 40 times higher than in extracellular fluid.
• High intracellular K^+ content is maintained due to active transport (through Na/K-ATPase).
• Potassium plays the defining role in a cell bioelectrical activity and maintaining of neuromuscular irritability and conductivity. Potassium daily maintenance in human is 2.5-5 g or 0.7-0.9 mmol/L/day. Total body potassium contain depends primarily on muscle bulk, in female it is lesser than in male; potassium concentration decrease is also observed in case of muscular atrophy. Potassium balance is defined by its intake and renal excretion. About 90% of entered into body potassium is excreted by kidneys, and the major portion is secreted by distal nephron. At the same time it is known, that potassium balance is based on the following mechanisms:
• in abnormal conditions acidosis contributes to intracellular potassium to hydrogen cations exchange (hyperkalemia), alkalosis favours hypokalemia;
• insulin and β-adrenergic effects contribute to potassium transport into cells, α-adrenoceptor agonists – to potassium backflow;
• mineralocorticoids or glucocorticoids excess intensify renal potassium excretion and influence potassium distribution between intracellular and extracellular compartments, accelerating its transport into cells;
• in the same cells of distal tubules simultaneously take place two oppositely directed processes: potassium reabsorption and secretion, that provides maximum potassium abstraction out of the urine in case of its blood deficiency, and in case of excess – potassium excretion[2];
• not only kidneys, but gastro-intestinal tract and perspiratory glands take part in potassium excretion.

In case of human body potassium deficiency, there occur disturbances of normal kidney function and histological changes gradually develop. Convoluted tubules become more stretched, nephrones become vacuolated. There is noted a significant decrease of renal concentrating ability, caused by the necessity of potassium ions restoring, and aciduria. Simultaneously, excessive sodium ion reabsorption takes place, this leads to its accumulation in the body. Homeostatic regulation of plasma potassium concentration is not so perfect, as one of, for example, sodium or glucose. Renal regulation mechanism efficiently prevents hyperkalemia, but much worse

works in conditions of hypokalemia. In clinical practice conditions accompanied by potassium deficiency are encountered more rarely, than hyperkalemia.

Causes of hyperkalemia development [3]:

1. Digestive tract

A. Decrease of dietary intake or inability to intake food

B. Digestive disorders (vomiting, diarrhea, villi adenoma, fistulas, ureter insertion into sigmoid colon) including ones of infectious origin

2. Kidneys

A. Metabolic alkalosis

B. Diuretics

C. Increased mineralocorticoid activity:

- primary (true) aldosteronism;
- secondary aldosteronism (including accelerated hypertension, Bartter's syndrome, tumor of juxtaglomerular apparatus cells);
- use of licorice preparations;
- glucocorticoid excess (Cushing syndrome, exogenous steroids, ectopic ACTH production).

D. Impairment of kidney tubules:

- renal tubular acidosis;
- leucosis;
- Liddle syndrome;
- antibiotics.

E. Magnesium deficiency

3. Hypokalemia due to potassium ions transport into cells (without general deficiency)

A. Hypokalemic periodic paralysis

B. Insulin effect

C. Alkalosis

D. Hypokalemia as a result of internal disbalance, in case of excessive potassium transport into cells from extracellular fluid (as during alkalosis, insulinotherapy or periodic paralysis).

Clinical presentation of hypokalemia is manifested like:

• Asthenia

• Neuromuscular disorders: muscle weakness, muscle cramps, paralyses, pareses, weak tendon reflexes, depression, catatonia, coma.

• Gastro-intestinal changes: meteorism, intestinal distention, paralytic ileus

• genitourinary system changes: urinary bladder atony, polyuria

• cardiovascular system changes: enlarged heart size, tachycardia, extrasystoles, hypotension

ECG changes:

• A-V-conduction disturbances

• Wide QRS-complex;

• QT elongation;

• ST-depression;

• U-wave presence (in V2-V3);

• T-wave flattens, becomes biphasic, negative;

• extrasystoles and paroxysmal tachycardia development.

Hypokalemia significantly increases risk of tachyarrhythmias development and is considered to be a life-threatening condition, especially in patients, who use cardiac glycosides. Severe hypokalemia leads to ventricular fibrillation and cardiac arrest.

Potassium deficiency leads to kidney sensitivity to ADH decrease and deteriorates concentration function. This can explain polyuria, that is often observed in patients with chronic potassium deficiency.

In case of potassium level decrease less than 3.5 mmol/L it is possible to talk about potassium deficiency and its correction necessity. Potassium level decrease less than 2.5 mmol/L requires prompt measures to normalize potassium level.

NB! It is important to remember, that general K^+ deficiency in organism can be accompanied by its decreased, normal or increased plasma content.

Daily K^+ urine excretion falls in case of hypokalemia. It should be noted, that potassium plasma concentration increase may be observed even in case of its general deficiency in organism.

Most commonly cardiovascular system becomes the target of hypokalemia. Long-term experience of "polarizing solution" appliance in cardiology showed its efficiency in complex treatment of different myocardial diseases. Mostly it is used for treatment of arrhythmias, caused by hypokalemia, including cardiac glycoside intoxication.

Most experimental, clinical and epidemiologic studies definitely confirmed positive effect of potassium on prevention and treatment of arterial hypertension and its complications – acute stroke. Additionally, medicinal treatment of AH can provoke hypokalemia worsening. First of all, we mean thiazide and thiazid-like drugs (hydrochlorotiaside, cyclometiaside) [3].

As the same proved fact it is possible to consider the influence of potassium blood concentration decrease on tachycardia, arrhythmias (cardiac fibrillation, ventricular premature beats and supraventricular arrhythmia), atrioventricular block development. Potassium preparations are the most popular drugs of the initial fluid management in patients with atrial fibrillation,

GIP infusion reduces ischemic damage and postischemic dysfunction during angina attack. In addition, it limits the size of infarction zone and facilitates recovery in postinfarction period.

because most cases of atrial fibrillation are caused in particular by hypokalemia. Potassium deficiency intensifies toxic action of digitalis preparations.

Birth of metabolic approach to CAD treatment traditionally is associated with glucose-insulin-potassium solution (GIP). Widespread long-term GIP use is based on switch effect of inefficient free fatty acids oxidation on damaged by hypoxia myocardium towards glucose, that is more favourable in conditions of hypoxia. Heart can be imagined as a pump with a "fuel", presented by carbohydrates (mostly glucose) and free fatty acids (FFA). In usual conditions initial glucose metabolism phase - anaerobic glycolysis leads to synthesis of small (less than 10%) ATP amount. In case of sufficient oxygen support main myocardial energy substrate are FFA, that provide 60-80% of ATP [4]. It is important to note that FFA is a less efficient energy source, comparing to glucose, because they require 10% more oxygen for the same amount of ATP production. In case of moderate ischemia FFA and glucose oxidation is decreased. Glycolysis becomes the main source of ATP. In such conditions glycogen storages are mobilized to support glycolysis. GIP has one more useful effect – ability to inhibit adipocytes FFA release (insulin action), that leads to FFA concentration decrease in area of stunned myocardium. So, improvement of energetic myocardial metabolism in conditions of ischemia is provided due to:

• Increased provision of glucose to myocardium → glucose oxidation stimulation [5];

• Inhibition of adypocytes FFA release → decrease of FFA concentration in area of stunned myocardium [6].

Last studies data prove that glucose-insulin-potassium is efficient in case of ischemic left ventricle dysfunction. Left ventricle dysfunction, caused by chronic ischemia becomes less pronounced during administration of glucose-insulin-potassium (reported in January issue of Heart, 2004). GIP infusion reduces ischemic damage and postischemic dysfunction during angina attack. In addition, it limits the size of infarction zone and facilitates recovery in postinfarction period. The similar metabolic interventions were not properly studied earlier.

Dr. Thomas Marwick and his colleagues (Queensland University, Brisben, Australia) studied effect of 5-hours long GIP infusion in patients with ischemic left ventricle dysfunction. Participants also underwent routine dobutamine stress echocardiography.

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Indices of left ventricle motility similarly increased in case of dobutamine administration (1.78 to 1.64) as well as in case of GIP administration (1.76 to 1.66). Peak systolic velocity also increased similarly: from 2.5 to 3.1 m/sec and from 3.0 to 3.5 m/sec respectively. GIP administration efficiency was especially pronounced for segments with restored "viability" according to dobutamine stress echocardiography results. Only in 5% of all 162 segments it was not found any contractile reserve.

End-systolic volume values slightly improved after GIP administration in 25 patients, and end-diastolic volume and ejection fraction remained the same. "We just wanted to confirm the hypothesis, that change of metabolism can improve cardiac function. According to our data, this is the first study of metabolic therapy during chronic CAD, - said Thomas Marwick, we need new efficient drugs, that influence myocardial metabolism in particular, and can be especially useful in patients, in whom it is impossible to perform revascularization".

LLC "Yuria-Pharm" manufactures finished pharmaceutical product, intended to liquidate organism potassium deficiency. G&P - solution for infusion, 100 mL of which contain potassium chloride 0.5g (potassium ion 67.06 mmol/L; chloride ion - 67.06 mmol/L), glucose – 5g, that corresponds to 0.5% potassium solution in 5% glucose solution. From one point of view GIP eliminates body energy losses, and from other one – compensates potassium losses. However, it is important to remember, that if G&P is used without insulin, infusion rate should not exceed 2-3 mg/kg/min.

Finished pharmaceutical form advantages are: high microbiological purity of drug, elimination of contamination risk during its preparation ex tempore, usability. Often "polarizing solutions" preparation is done under conditions of time shortage. This leads to irregular distribution of potassium chloride solution in the volume of infusion medium and can cause complications, similar to intravenous administration of concentrated potassium chloride solution. Infusion solution G&P is free from this disadvantage. Only in conditions of modern pharmaceutical factory it is possible to provide stringent control of qualitative and quantitative infusion solution composition.

List of references is in editors office.