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Using biochemical approaches for the choice of auxiliar substances and establishing the composition of medicinal preparations

Zastosowanie podejścia biochemicznego w wyborze substancji pomocniczych i ustalaniu składu preparatów leczniczych

In accordance with normative documents which regulate registration of medicinal preparations, a registration dossier on the preparation must contain information about research from pharmaceutical development, in particular, the composition and explanation of the function of each component in the composition of medicinal preparation with the justification of its inclusion must be described. In some cases, experimental information is needed for the choice of components, for example for antimicrobial preservatives, in others – the choice must be grounded by sending the proper scientific literature or by combination of the two approaches [4, 5].

The aim of our work was to study the application of literature information on the results of biochemical research for determination of the composition and choice of auxiliary substances in the process of development of medicinal preparations.

The production of effective medicinal preparations needs application of plenty of auxiliary substances, different by nature, properties and functional purposes. Auxiliary substances are an important biopharmaceutical factor in the technology of medicinal preparations [3, 5, 10]. The nomenclature of auxiliary substances which are used in the technology of medicinal preparations depends mostly on the method of application of medicinal preparation and the dosage form. Hence, nomenclature of auxiliary substances for parenteral preparations is minimum, while nomenclature of the last in medicinal preparations for local application is extraordinarily large and considerably prevails the nomenclature of auxiliary substances for oral preparations [3, 9].

Depending on the type of dosage form, the nomenclature of auxiliary substances changes substantially. For example, in the composition of powders excipients are used sometimes colouring matters and flavouring agents; in liquid forms – solvents, antimicrobial preservatives, antioxidants and other excipients such as dispersing, suspending, thickening, emulsifying, buffering, flavouring and sweetening agents and colouring matter; in eye drops – substances to adjust the tonicity or the viscosity, to adjust or stabilize the pH, to increase the solubility of active ingredients or to stabilize the preparation [3, 5, 9].

With the identical functional purpose, but in different dosage forms, different auxiliary substances can be applied. Hence, with the function of pH correction in infusions only hydrochloric acid, or sodium hydroxide can be used. Using other inorganic acids and alkalis, in particular sulphuric or phosphoric acids, potassium hydroxide are not permitted, as such use can result in a substantial

increase in the plasma of sulphate, phosphate ions or ions of potassium. Nomenclature of pH regulators in semi-solid preparations is wide enough for sorbic and boric acids, sodium tetraborate, potassium hydroxide, triethanolamine and others. As far as possible, dosage forms for oral application are necessary to stabilize by organic acids, the anions of which are submitted to metabolism, because non-metabolizable chloride-anion have acidic action [2]. Solutions of essential amino acid of lysin and histidine are not expedient to stabilize by hydrochloric acid through the danger of the rise of the acidosis [2].

With the purpose of diminishing oxidation of active ingredients in dosage forms such antioxidants as sodium or potassium sulphite, hydrosulphite or metabisulfite are used. The substantial lack of acid sulphites is their capacity for active cooperation with amino acid, especially with cysteine, methionine, tryptophane, as a result of which non-active or harmful for the organism compounds are formed. Acid sulphites also react with bases of nucleic acids and they have potential mutagenicity. In this connection, these antioxidants are not expedient to use for stabilizing of parenteral preparations, which are entered in the organism in large volumes [10].

It is not recommended to use benzyl alcohol in parenteral preparations, intended for application to the children under 2 years old, because the product of decomposition and metabolit of benzyl alcohol is benzaldehyde, which is toxic to central nervous system [5].

A striking example of establishing the composition of medicinal preparations on the basis of acid-base equilibrium indexes and electrolyte balance of organism are solutions for peritoneal dialysis (PDS).

First of all, peritoneum serves as a natural selective permeable exchange membrane, through which using dialysis solution extrarenally it would be possible to take out from an organism excess of water, electrolytes, products of metabolism, toxins which accumulate in blood of patients with acute or chronic kidney insufficiency, and also factors of exogenous intoxication, it is necessary that electrolyte composition and pH of peritoneal dialysis solutions are near to normal electrolyte composition and pH of blood of organism [8]. Taking into the consideration that pH of the internal environment of organism is in narrow limits – 7.35–7.45, and displacement of pH of plasma higher than 7.8 or below 6.8 not consonant with life, the optimum value of pH for PDS is within a range 7.3–7.5. Except that, such a value of pH for these solutions does not negatively influence the monolayer of cells of mesotelium of peritoneum [1, 7].

In the extracellular liquid and blood a leading role in supporting the constancy of pH belongs to the bicarbonate buffer which consists of carbonic acid and sodium bicarbonate, and which changes rapidly and represents the state of other buffer systems of acid-base equilibrium. Therefore, taking into consideration the normal limits of vibrations in plasma and intercellular liquid of standard bicarbonate (SB) 22.0–28.0 mmol/l, the content of sodium bicarbonate in PDS must be within the limits of 20–30 mmol/l [6, 8].

For the biosynthesis of hydrocarbonate and also the binding of the acids formed in the process of metabolism in solutions for peritoneal dialysis, sodium salts of weak acids with pKa $\leq$5 are added. It is recommended that these acids are chosen from the following group of acids: lactic, piruvic, citrate, isocitrate, cysisocitrate, α-ketoglutarate, succinate, fumarate, malate or oxaloacetic, as these acids are formed in the Krebs cycle and are related to the organism [8].

Taking into consideration the electrolyte composition of plasma and intercellular liquid, and also diminishing of excretion of electrolytes and water in chronic kidney insufficiency, the content of ions of sodium in PDS must be within the limits of 130–140 mmol/l, ions of calcium and magnesium 0–2.0 mmol/l, ions of chloride 90–100 mmol/l. With the purpose of avoiding hyperkalemia which accompanies chronic kidney insufficiency, salts of potassium enter in the complement of PDS.

With the purpose of diminishing the oxidizing termodestruction of glucose in PDS such technological reception as satiation of solution by rare gas is applied; however, it is necessary to take into account the fact that the concentration of carbon dioxide does not have to exceed its maintenance in tissues [8].

Thus, establishment of the composition of medicinal preparations and the choice of auxiliary substances are based above all things on the results of biochemical studies taking into account that to provide an effective and safe action, foremost medicinal preparations must not damage the basic indexes of acid-basic equilibrium and electrolyte balance of organism

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SUMMARY

The nomenclature of auxiliary substances which are used in the technology of medicinal preparations depending on the method of application of preparation and the dosage form is presented. The choice of auxiliary substances on the basis of literature information on biochemical researches is justified. An example of determining the composition of solutions for peritoneal dialysis on the basis of of acid-base equilibrium indexes and electrolyte balance of organism is given.

STRESZCZENIE

W pracy przedstawiono nomenklaturę substancji, które są stosowane w produkcji preparatów leczniczych w zależności od sposobu podawania i formy dawkowania. Na podstawie pochodzących z badań biochemicznych informacji z piśmiennictwa został ustalony proces doboru substancji pomocniczej. Jako przykład zastosowania tego podejścia przedstawiono proces ustalania składu płynu do dializy otrzewnowej na podstawie wyników badania wskaźników równowagi kwasowo-zasadowej i wodno-elektrolitowej.