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ACID ION MODIFICATION IN A DIALYSIS FLUID

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Apart from its main electrolytes – sodium, potassium, calcium and magnesium – a dialysis fluid (DF) contains a buffer for correction of acidosis. A small amount of acid is added to the DF to prevent calcium and magnesium precipitation. Acetic acid has traditionally been used for this purpose. Several studies have shown that acetate ion, even in small concentrations, can cause a number of adverse events, such as low blood pressure, production of proinflammatory cytokines, etc. This literature review aims at considering alternative acidic components of DF, such as citric, hydrochloric, and succinic acids, as well as their advantages, possibilities and features of their use in wide clinical practice.

Keywords: dialysis fluid, acetate, citrate, hydrochloride, succinate.

INTRODUCTION

In hemodialysis, the patient's blood contacts the dialysis fluid (DF or dialysate) through the membrane; transmembrane metabolism is the primary physical mechanism behind the method. DF contains the main electrolytes, which are balanced in concentrations with human plasma – sodium, potassium, calcium and magnesium (in the form of chlorides), as well as a buffer designed to correct acidosis. Since kidney failure is characterized by deficit of bicarbonate, the main buffer system, there should be direct replacement of this deficit during treatment. Accordingly, dialysate contains bicarbonate in a concentration exceeding the physiological level (about 32 mmol/L). Bicarbonate liquid needs to be stabilized to prevent precipitation of hardness salts (calcium and magnesium carbonates) and bring the pH to physiological values. Before hemodialysis came onboard, this problem was addressed by saturating DF with carbon dioxide, passing carbon dioxide through it (Fig. 1).

Due to the technical complexity of this approach with the introduction of long-term hemodialysis, bicarbonate was replaced by acetate as the buffer system in the dialysate. The use of stable acetate-based dialysate prepared from a single-component concentrate has greatly simplified the technical implementation of hemodialysis. How-

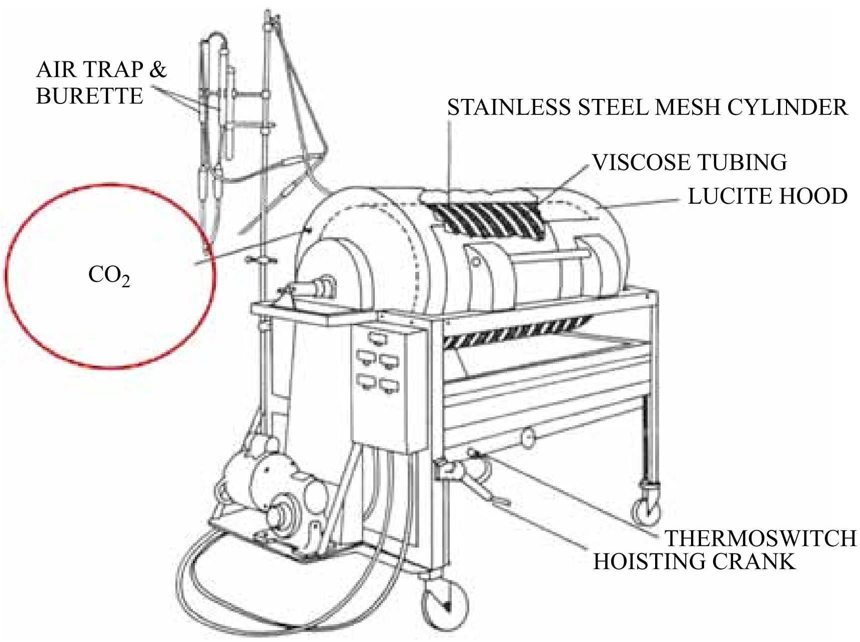

Fig. 1. Stabilization of bicarbonate dialysis fluid with carbon dioxide in one of the first hemodialysis systems (Kolff–Brigham artificial kidney, 1948

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ever, from a clinical point of view, acetate has proven to be unfavorable. In the absence of bicarbonate in DF, its concentration was reduced in the blood plasma after commencement of dialysis, and the absence of sufficient carbon dioxide tension in the solution caused hypoxemia. In addition, high acetatemia, progressing during hemodialysis, was complicated by numerous episodes of intradialytic hypotension associated with peripheral vasodilation [1] and by reduced myocardial contractility. As a result, bicarbonate was reintroduced as the main buffer in dialysis fluids in hemodialysis in the 1980s. The problem of dialysate stabilization was solved by dividing the dialysis concentrate into two components, one of which contained sodium bicarbonate, and the second was added with acid. When mixed in a proportional system, part of bicarbonate ions reacts with hydrogen ions to achieve sufficient carbon dioxide tension and stabilize DF acidity at a level that prevents calcium and magnesium salt precipitation.

NECESSARY CLARIFICATION

Thus, from a chemical point of view, carbonic acid is the only acid that must be present in a dialysate. However, this substance has an extremely low melting point and is characterized by very high volatility at atmospheric pressure. In order to obtain carbonic acid in a solution, you either saturate the liquid with carbon dioxide gas (Fig. 2, a), or obtain carbonic acid in a chemical reaction of bicarbonate with protons, as is the case in modern hemodialysis machines (Fig. 2, b).

The need to deliver hydrogen ions to the DF is why an acid is added to it. The negative ion in the acid composition is only an additive that you have to bear with. Depending on its chemical composition, this ion can play both a positive and a negative role in the body.

ACETATE ION

Compared to acetate-containing bicarbonate dialysate, the content of acetate ion in modern bicarbonate dialysate is an order of lower magnitude, = 3–6 mmol/L, depending on the DF acidification method. In the patient's body, acetate ion is metabolized in the liver and muscles to form an equivalent amount of bicarbonate. Some acetate ions are conjugated with coenzyme A, which requires conversion of adenosine triphosphate (ATP) to cyclic adenosine monophosphate (cAMP). cAMP triggers nitric oxide (NO) production and vasodilation. In addition, acetate ion stimulates production of potent proinflammatory cytokine interleukin-1. There are no clear indications of the clinical consequences of the influence of trace amounts of acetate. Nevertheless, it is assumed that for certain categories of patients, such effects is irrelevant as confirmed by some studies on acetate-free methods [2, 3].

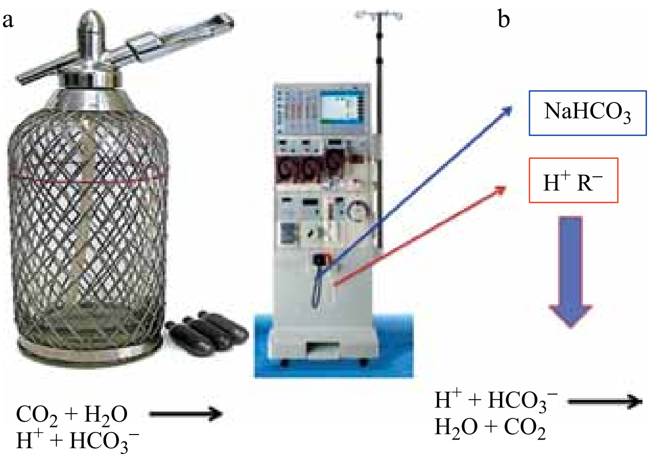

Fig. 2. Carbonic acid production in a solution

CHLORON ION

Since all the electrolytes in a dialysate solution are in the form of chlorides, total concentration of chlorine ions is very high, about 108 mmol/L. It is therefore logical to use hydrochloric acid for DF acidification. A 3 mmol/L increase in concentration of chlorine ions has no effect on the patient's body. At the same time, such DF does not contain any extraneous anions, including acetate ion. A large observational study conducted in France, which included data from over 15,000 patients, showed improved survival in patients aged 70 years and older who have never come in contact with acetate ion-containing DF [4]. A team of authors [2] showed that the use of acetate-free bicarbonate dialysate with slow continuous dialysis in patients with acute kidney injury after cardiac surgery was able to reduce the rate of hemodynamic complications by 3.8 times in comparison with standard acetate-containing bicarbonate dialysate. The use of standard bicarbonate dialysate was associated with 12-fold increased acetate ion concentration in blood plasma from the upper limit of the norm [2].

Widespread use of hydrochloric acid concentrate in common hemodialysis is obviously limited by the technical difficulties associated with the aggressiveness of hydrochloric acid. Nevertheless, such concentrates today are available including in the domestic market, and one can expect an increase in their use.

CITRATE ION

If hydrochloric acid in dialysate solution can be considered intact with respect to metabolic processes in the body, then if acetic acid is partially or completely substituted with citric acid in the dialysate, there could be certain positive effects. In an energy-free metabolic process, 1 mmol of citrate produces 3 mmol of bicarbonate. Moreover, citrate metabolism is adequate not only for renal but also for liver failure, as shown by studies on citrate anticoagulation in the treatment of critically ill patients [5–7]. Citrate was found to have a positive effect on exercise tolerance in healthy volunteers [8]. *In vitro* experiments have shown that citrate causes less activation of complement and granulocytes in comparison with acetate [9–11], and also reduces the severity of oxidative stress [12–14]. Besides, citrate has been widely used as an anticoagulant since 1914. Thus, when using this ion in a DF composition, one can naturally expect decreased need for anticoagulation in the extracorporeal circuit, as well as certain optimization of metabolic processes.

Several studies have shown that heparin dose can be reduced when using a citrate-enriched dialysate. So, Sands et al. showed that one-third reduction in heparin when using dialysate containing citrate does not increase prevalence of thrombosis in the extracorporeal circuit and is not associated with decreased dialysis efficiency [15]. When comparing heparin-free dialysis with periodic flushing of the extracorporeal circuit with dialysis, performed with citrate-enriched dialysate, there was no difference in the incidence of thrombotic complications [16]. The most encouraging results were obtained by Aniort et al. When performing online hemodiafiltration without using anticoagulant, the use of citrate-enriched DF prevented thrombosis in the extracorporeal circuit during 120 treatment sessions [17]. In yet another study [18], citrate was found to have a moderate anticoagulant effect. Besides, the authors noted decreased pre-dialysis levels of C-reactive protein and beta-2 microglobulin, absence of post-dialysis hypocalcemia and moderate concentrations of citrate ion (0.29 mmol/L at a concentration safe for regional citrate anticoagulation = 0.89 mmol/L). Decreased concentrations of C-reactive protein and beta-2 microglobulin was also noted when using citrate-based dialysate for hemodiafiltration [19]. Within 4 months after transferring 29 patients to maintenance hemodialysis with citrate-containing dialysate, Kuragano et al. noted that predialysis bicarbonate levels normalized in patients with initially low serum bicarbonate, the need for erythropoiesis-stimulating agents decreased and albumin levels increased. All positive changes disappeared after patients returned to treatment with standard acetate-containing dialysate [20]. Better acid-base correction with citrate-containing dialysate has been noted in several studies [21–23]. In addition, the authors note a regular decrease in post-dialysis levels of ionized calcium, and, accordingly, a certain increase in parathyroid hormone levels. Such observations are not universal, since in the already mentioned Panichi et al. [18], where dialysate calcium concentration was 1.5 mmol/L, hypocalcemia was not detected. The clinical consequences of the chelating ability of citrate with respect to calcium ions are not yet clear. Some authors suggest that standard concentrations of calcium and magnesium should be reviewed under the use of citrate-containing dialysate [21].

SUCCINATE (AMBER ACID)

In Russia, the acid component of bicarbonate concentrate has been industrially produced for several years. Here, acetic acid is partially, and in recent years, completely replaced with succinic acid. When using this prescription of concentrate in the clinic, there was decreased pre-dialysis sodium levels and systolic blood pressure along with decreased interdialysis hydration and severity of intradialysis hypotension. In addition, there was moderate increase in hemoglobin levels. The authors attribute such effects to the influence of succinate on angiogenesis, which allows mobilizing osmotically inactive sodium ions and making them available for excretion during hemodialysis [24]. Unfortunately, the experience of using succinate-containing dialysate and reports on this topic are very scarce and limited only to national sources.

CONCLUSION

Dialysate solution along with the dialysis membrane form the basis of hemodialysis system, which determines substance transfer patterns during treatment sessions. However, while many studies have been devoted to the study of the properties of dialysis membranes and their effect on dialysis therapy, there is substantially less amount of information on DF. To a certain extent, this is due to widespread introduction of central concentrates delivery systems for hemodialysis. Here, clinicians are limited typically to choosing between only two prescriptions. Nevertheless, excluding acetate ion from dialysate through the use of hydrochloric acid does not require any changes to the existing practice at dialysis centers. Due to the increasing elderly population and consequently, comorbidity of dialysis patients, such conversion seems very urgent. Clarifying the indications for the use of citrate-containing dialysate and determining its optimal composition require further research.

Thus, the process of driving out acetate ion from the commonly used dialysate solution, which began with widespread withdrawal from single-component acetate concentrate, is ongoing. In order to speed up this action and make it more meaningful, research in this direction should be intensified.

The authors declare no conflict of interest.

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