Model-Based Analysis of Na-K+ Pump Influence on Potassium Depuration during Acetate Free Biofiltration (AFB)

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Abstract

Potassium ion (K^+) kinetics in intra and extracellular compartments during hemodialysis was studied by means of a double-pool computer model which included potassium-dependent active transport (Na-K-ATPase pump) in thirty-four patients (21M/13F; aged 66 ± 22 years old, dry weight 68 ± 18 kg, height 160 ± 15 cm) on renal replacement therapy with thrice weekly 4 hour double-needle hemodialysis.

Each patient was studied during acetate free biofiltration (AFB) with a constant K^+ dialysate concentration (K_{CONST} therapy) and with a time-varying (profiled) K^+ dialysate concentration (K_{PROF} therapy). The two therapies induced different levels of K^+ plasma concentration (K_{CONST}: 3.6±0.8 vs. K_{PROF}: 4.0±0.7 mmol/L, time-averaged values, $p<0.01$).

The computer model was tuned to accurately fit plasmatic K^+ measured in the course of K_{CONST} and K_{PROF} therapies and was then used to simulate the kinetics of intra and extracellular K^+. Model-based analysis showed that almost all the K^+ removal in the first 90 minutes of dialysis was mainly derived from the extracellular compartment. The different K^+ time course in the dialysate and the consequently different Na-K pump activity resulted in a different sharing of removed potassium mass at the end of dialysis: 55±17% from the extracellular compartment in K^+_{PROF} vs. 41±14% in K^+_{CONST}.

These results suggest that the Na-K pump plays a major role in K^+ apportionment between extracellular and intracellular compartments, and potassium dialysate concentration strongly influences pump activity. For this reason the computer-model here presented may represent a useful tool to quantitatively assess the impact of dialysate potassium on K^+ kinetics in intra and extracellular compartments and to design dialysate potassium content tailored to the patient's needs.

1. Introduction

End stage renal disease (ESRD) patients treated by maintenance hemodialysis regularly undergo K^+ overload due to dietary intake in the interdialysis period. In order to re-establish a physiological K^+ plasma concentration, 80-100 mmol of K^+ are quickly removed during the treatment. Hemodialysis removes K^+ from the extracellular compartment, but more than 60% of the potassium mass removed derives from the intracellular compartment [1]. As consequence the K^+ exchange mechanism between intra-extra compartments plays a pivotal role in K^+ removal. The K^+ shift through the cellular membrane follows passive diffusion from the intra to the extracellular compartment and, in the opposite direction, the active transport due to the Na-K ATPase transporter (Na-K pump). We developed a computer model of the K^+ kinetics during hemodialysis to better understand the role of passive and active mechanisms in the K^+ removal process.

2. Methods

Thirty-four patients (21M/13F; aged 66 ± 22 years old, dry weight 68 ± 18 kg, height 160 ± 15 cm) on renal replacement therapy with thrice weekly 4-h double-needle hemodialysis at the dialysis units of four centres were enrolled.

Acetate-free biofiltration (AFB) with constant ($K+_{CONST}$) and profiled ($K+_{PROF}$) dialysate potassium were administrated. AFB is an hemodiafiltration technique combining diffusion with convection with buffer-free dialysate [2, 3]. Acidosis correction is obtained via post dilution intravenous infusion of a sterile

pyrogen-free sodium-bicarbonate solution (145 mmol/L). The infusion flow rate was adjusted depending on the patient's needs and on the concentration of the infusion solution. With 145 mmol/L infusion bags the infusion flow rate was generally set to 2–2.4 l/h. In the $K+_{CONST}$ therapy, the dialysate K^+ concentration was fixed at 2.5 mmol/L. Conversely, in the $K+_{PROF}$ therapy, the dialysate potassium concentration changed during the session according to a decreasing profile.

Potassium mass was assumed, in line with previous studies [4], to be distributed in two major volumes: the intracellular (V_{ic}) and the extracellular one (V_{ec}). The extracellular volume consists of interstitial fluids and plasma water. The intracellular volume represents the whole content of the cells. The changes in extracellular potassium mass (M_{Kec}) were assumed to be determined by three fluxes: a) a diffusive flux (J_{Diff}) that moves K^+ from the intracellular to extracellular space proportionally to the gradient between the intracellular K^+ concentration (M_{Kic}/V_{ic}) and the extracellular one (M_{Kec}/V_{ec}); b) an active flux (J_{pump}), caused by the Na^+-K^+ pump, that shifts the K^+ ions from the extracellular into the intracellular compartment; c) an outward flux (J_K) accounting for the removal of K^+ from the extracellular space through the dialysis filter.

3. Results

The initial K^+ plasma concentration was similar at the beginning in the two treatment modalities (about 5.5 mmol/L). However, it was observed since 15 up to 90 minutes a higher K+ concentration was found in K^+_{PROF} therapy that became similar to the other modality only at the end-dialysis (3.3±0.3 mmol/L in K^+_{CONST} vs. 3.2±0.4 mmol/L in K^+_{PROF} , NS). The difference in K^+ plasma concentration between K^+_{CONST} and K^+_{PROF} was summarized by considering the time-average value that was significantly lower in K^+_{CONST} than in K^+_{PROF} treatment (3.6±0.8 vs. 4.0±0.7 mmol/L, $p<0.01$). Regarding others clinical measurements no differences were found in pH, sodium plasma concentration and weight loss.

The K^+ plasma concentration predicted by our kinetic model reproduced the measured values fairly well. The overall comparison of measured and predicted data disclosed a good correlation ($r = 0.93$). More than 60% of differences between measures and predictions were within 0.03±0.3 mmol/L which is comparable with the accuracy of electrolytes analyzer used. The average prediction error in this group was relatively low (0.06±0.3 mmol/L).

One example of model fitting of two different therapies for the same patient is shown in Fig. 1. Regarding the model identification between the two therapy only the model parameter, which account for the inward K^+ mass flow due to the Na^+-K^+ pump was found significantly different (K^+_{CONST}: 0.9±0.4 vs. K^+_{PROF} :0.6±0.3, $p<0.01$).

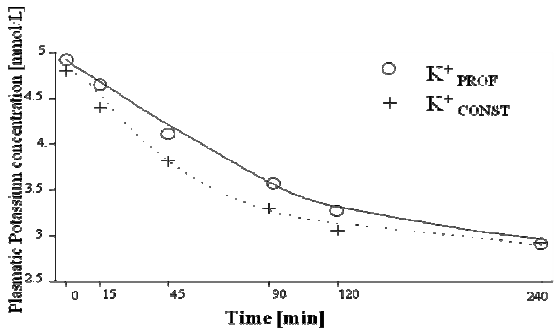

Fig. 1: example of model fitting of the experimental potassium plasma concentration during K^+_{CONST} (+) and K^+_{PROF} (o) treatments on the same patient

The different Na-K pump flow highlighted by the model parameter within the different K^+ time course in the dialysate resulted in a different sharing of removed potassium mass. More specifically, the model predicted that 55% of potassium was removed from the extracellular compartment (49±26 mmol over a total removal of 88±39 mmol) in K^+_{PROF} therapy, whereas only 41% of potassium was removed from the extracellular compartment (40±20 over 97±34 mmol) in K^+_{CONST} therapy.

4. Discussion and conclusions

Model-based analysis showed that the changes in plasma K^+ concentration occurring during the treatment largely modulated Na-K pump activity. The dependence of Na-K pump activity on the extracellular K+ concentration is well-known but often underestimated when the mechanisms underlying K+ changes in the course of hemodialysis are assessed [5].

During our study K^+_{PROF} therapy determined higher K^+ removals from the extracellular compartment at the end of treatment with respect to K^+_{CONST}. Since factors affecting pump activity such as pH, sodium plasma concentration did not exhibit significant differences between K^+_{CONST} and K^+_{PROF} therapies, we justified this result on different pump activity assessed by model parameter. This observation is important since dialysis techniques with tailored potassium removal have recently been proposed to combine adequate potassium removal with a reduced risk of malignant arrhythmias in chronic dialysis patients who exhibit an increasing incidence of cardiac comorbidities [6]. Our kinetic model could be a

way to better understand the mechanisms of potassium regulation to developed new methods of potassium profiling dialysate. In this way, it would be possible to achieve a target potassium removal without induce extreme alterations of resting potential membrane link to plasmatic potassium concentration that can have an impact in patients with risk for cardiac arrhythmias [7].

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