Do not forget to individualize dialysate sodium prescription

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Sodium mass balance in haemodialysis

Sodium mass balance is primarily dependent on two factors: dietary salt intake and sodium removal during haemodialysis (HD). Salt intake during the interdialysis period is dependent on patient behaviour and is a strong driver of volume overload [1]. The average American consumes ~149 mmol/day [2]; most Western societies consume between 150 and 250 mmol/day [3]. There is evidence that HD patients ingest similar amounts of sodium. A small series of Spanish HD patients showed baseline sodium intake of ~173 mmol/day [4]. Likewise, a study of 28 English HD patients showed an average estimated sodium intake of 251 mmol/day [5].

Sodium load in HD patients is associated with thirst, fluid retention, interdialysis weight gain (IDWG) and hypertension [6]. Therefore, one of the most important goals of the dialysis therapy is to remove exactly the mass of sodium that has been accumulated in the interdialysis period in order to reach a zero sodium mass balance. Sodium removal during HD can occur through convection and diffusion. Current prescribing practices for chronic intermittent HD rely primarily on convective losses (≈78%) and less on diffusive losses (≈22%) [5]. This relative distribution, however, is dependent on the amount of ultrafiltration occurring during any given HD session (i.e. convective losses) and the prescribed dialysate sodium concentration and its relationship with patient’s own plasma sodium (i.e. diffusive losses). The diffusive gradient between plasma and the inlet dialysate sodium concentration is an important factor in the ‘fine tuning’ of sodium balance in bicarbonate HD [1].

The inlet dialysate sodium diffusive concentration gradient

In this issue of Nephrology Dialysis and Transplantation, Munoz Mendoza et al. [7] provide further evidence of the statistically significant and clinically meaningful association between sodium diffusive gradient and IDWG in a large set of clinically stable patients on HD. Actually, this association had been shown in previous studies [8–10].

If ‘high’ and ‘low’ sodium dialysis have specific ‘pharmacologic’ effects, then, what would happen if a ‘eunatraemic’ dialysate were used? Eunatraemic dialysis means neutralizing the diffusive sodium concentration gradient across the dialysis membrane to eliminate diffusive sodium fluxes. Achieving eunatraemic dialysate involves recognizing that each dialysis patient has a unique ‘set point’ for plasma sodium [10–12], that this set point is actively defended [13] and that the plasma sodium concentration is different from the eunatraemic dialysate sodium concentration [10,12,13]. Munoz Mendoza et al. [7] confirmed some important observations about sodium set point and sodium gradient. They showed that (i) the mean pre-HD plasma sodium concentration in 1084 clinically stable HD patients was 136.7 ± 2.9 mmol/L and 83% of them had pre-HD plasma sodium concentration lower than 140 mmol/L, i.e. the most common dialysate sodium prescription; (ii) the mean sodium gradient was 4.6 ± 4.4 mmol/L (range from −7 to 24 mmol/L) and the mean IDWG was 2.8 ± 1.1 kg (range from −0.7 to 7.2 kg) with a direct correlation between IDWG and sodium gradient; (iii) no higher frequency of intradialysis hypotension was shown in patients with sodium gradient ≤0 compared with patients with positive sodium gradient.

What concentration of dialysate sodium prevents diffusive sodium transfer across the dialysis membrane? The diffusible sodium concentration is determined by the plasma water sodium activity, the charge characteristics, quantity of non-membrane permeable plasma proteins (the Gibbs–Donnan effect), the pH gradient across the dialysate membrane and the sodium reflection coefficient of the dialysis membrane. Together, these dynamic variables determine the dialysate sodium concentration that will prevent diffusive sodium transport [13]. This typically results in a ‘eunatraemic’ dialysate sodium concentration of 1.5–5 mmol below the plasma concentration reported by flame photometry or indirect potentiometry [13]. However, direct potentiometry is currently the best method to determine the plasma and dialysate sodium concentration, as it permits the determination of sodium concentration in undiluted samples and is not influenced by abnormal levels of plasma proteins and lipids [14]. Furthermore, the method measures non-complexed free sodium concentration, which represents those sodium particles available for diffusion [14]. For this reason, it is proposed that sodium
levels determined by direct potentiometry be referred to as the concentration of ionized sodium rather than total sodium concentration [14]. Thus, direct potentiometry measures ionized plasma water sodium concentration in the blood and ionized sodium concentration in the dialysate. In such a case, the Gibbs–Donnan correction is not needed for plasma sodium and a dialysate to plasma sodium gradient may be established directly [8].

In conclusion, analytical performances of both direct and indirect potentiometry are in all cases satisfactory and therefore could be used in both normal and pathological ranges, being aware that these differences in methodology should be taken into account to explain discrepancies between results, such as in the case of pseudohyponatraemia [15].

The need for dialysate sodium individualization

The concept of an individual and relatively ‘fixed’ osmolar set point in HD patients is crucial to understand sodium mass balance in HD. Humans have mechanisms to preserve their extracellular osmolality towards a seemingly fixed set point, and it appears that HD patients also maintain a fixed osmolar set point despite the loss of kidney and vasopressin feedback mechanism [16]. Such set point is clearly shown in studies by Peixoto et al. and Flanigan [11,12]. Furthermore, pre-HD plasma sodium concentrations are quite reproducible, suggesting that there is a preferred plasma sodium concentration in individual HD patients [10]; furthermore, plasma sodium concentration in HD patients is stable in long-term observations [11] and is normally distributed [17].

The need for dialysate sodium individualization is largely ignored. Commercial dialysate provides a limited choice of sodium concentrations and each facility tends to use a single sodium concentration and consider it as ‘standard’, i.e. within most dialysis facilities some nominal value of dialysate sodium is used for all patients [13]. On the contrary, an individualized dialysate sodium prescription should lead to a better management of IDWG, thirst and blood pressure [8,18]. Prescribing dialysate sodium concentration with pre-HD plasma sodium as a reference seems reasonable to achieve this goal [18]. The same is applicable to the individual ultrafiltrate sodium concentration, which would represent the actual diffusible sodium in plasma water [13]. However, changes in plasma sodium activity occur along HD sessions, and serial determinations of sodium concentration in plasma or ultrafiltrate during HD sessions are impracticable.

Non-osmolar sodium storage and possible implications in HD sodium mass balance

Hitherto, sodium mass balance in HD has been interpreted as a two-compartment model for sodium and water balance [19]. However, the model has been challenged by Titze [20], who has shown that sodium may accumulate without associated water retention and suggested that interstitial tonicity is regulated by tissue-specific molecular mechanisms. According to these findings, the skin is a major place for osmotically inactive sodium storage [21], where negatively charged glycosaminoglycans function as binders [22]. Whether this phenomenon occurs in dialysis patients is not known; along these lines, the possibility that the ‘lag phenomenon’, i.e. the reduction in blood pressure in HD patients that occurs months after dry weight achievement, could be related to a rise in inactive sodium storage was evoked [23]. In favour of this hypothesis, a study that analysed changes in total body water resulting from lowering dialysate sodium concentration showed a strong trend towards blood pressure fall despite minimal changes in extracellular water measured by bioimpedance [24].

Conclusions

The demonstration of a fixed and individual osmolar set point in HD patients indicates that emphasis on dietary sodium restriction will avoid excessive IDWG. It also predicts that a euonaemic dialysate prescription will prevent unnecessary sodium loading and its consequent fluid ingestion and interdialysis hypertension. These tasks can be achieved in current HD practice by adequate dietary counselling and individualized dialysate sodium prescription [3,18].

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References

The never-ending search for the perfect dialysis. Should we move from the best treatment to the best system?

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The history of dialysis may be seen as a history of the search for the perfect treatment, combining quantity and quality: ensuring a long life, limiting the impact of the disease and its therapies. Since the start of renal replacement therapy (RRT), each new treatment or schedule has been compared with the previous ones, i.e. peritoneal dialysis (PD) versus haemodialysis (HD), bicarbonate versus acetate, haemodiafiltration versus haemodialysis, long versus short, daily versus intermittent [1–3]. Comparisons have led to context-sensitive, often conflicting results [4,5]. The continuous evolution of treatments has added further confusion. Hence, the search for the perfect dialysis is an unmet goal and a continuous task for the medical community. The paper by Ok et al. [6] is in line with this never-ending quest.

What do we mean by a dialysis treatment, and how do we measure its benefits?

Dialysis should not be defined as a treatment but as a system. It needs supplies: machines, filters, water and regulation of fluxes, electrolytes, ultrafiltration, anticoagulation. It needs a blood or peritoneal access and support therapies. Several of these elements have been shown to be significantly related to outcomes. However, no study will have the statistical power to take all of them into account. Theoretically, randomization could at least partly compensate for heterogeneity; however, randomization of the major dialysis treatments (PD versus HD) and of dialysis versus transplantation is clearly unethical, and even randomization of dialysis schedules may be difficult. Indeed, Ok et al., in line with other studies, reported that only a minority of their patients (287 of 1257 patients in 10 centres, 22.8%) was interested in experiencing a long, thrice weekly dialysis schedule [6,8]. Participation in a randomized control trial

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