Clinical Implications of the Relationship between Low Calcium Concentration Dialysate and Sudden Death

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In this issue of *CJASN*, Pun *et al.* (1) increase our understanding about the risk of sudden death associated with lower calcium dialysate concentrations. For many years, we have known that lower calcium dialysate concentrations are associated with a prolongation of the QT interval and QT dispersion (2)—both risk factors for sudden death (3). These changes in cardiac conduction were noted by Näppi *et al.* (2) when the dialysate calcium concentration was decreased from 1.5 mmol/L (3 mEq/L) to 1.25 mmol/L (2.5 mEq/L). The use of a lower calcium dialysate has also been associated with a statistically significant lowering of BP during the dialysis treatment (4). Because increased QT dispersion and lower BPs are associated with lower dialysate calcium concentration, one might suspect that low calcium dialysate would be associated with an increased risk of intradialytic cardiac arrest, and indeed, Pun *et al.* (5) had previously shown that lower calcium dialysate was associated with an increased risk of sudden death during the dialysis procedure. In this edition of CJASN, Pun *et al.* (1) extended their findings to show that the higher the gradient between serum calcium and dialysate calcium, the more likely it is that sudden death will occur.

Pun *et al.* (1) performed a case-control study of 510 patients who suffered cardiac arrest during the hemodialysis procedure and 1560 matched controls. Both cases and controls were obtained from a database of 43,200 patients who received hemodialysis between 2002 and 2005. The study revealed that low calcium dialysate (<2.5 mEq/L) was associated with a twofold increased risk of sudden death during the dialysis procedure (95% confidence interval=1.4–2.9). Higher corrected serum calcium and an increasing serum dialysate calcium gradient were also significant risk factors.

Sudden death events during dialysis are uncommon, estimated to occur between four and seven times per 100,000 dialysis treatments (5); therefore, the risk of sudden death during the dialysis treatment is very low. However, sudden death and cardiac events are the most significant cause of mortality in the dialysis population. The increased risk of sudden death occurs at the end of the weekend interval immediately before dialysis or within 12 hours of the start of a dialysis session (6). Although the dialysate calcium concentration is unlikely to be a risk factor for deaths occurring at the end of the weekend interval, it could very well contribute to the large number of deaths and cardiac events occurring in the hours after the dialysis session. In a study from our center, approximately one-third of all sudden deaths occurred within 12 hours of the start of the dialysis treatment (6).

There are several possible reasons why the high serum-to-dialysate calcium gradient may cause sudden death. The most likely possibility is that the larger serum-to-dialysate calcium gradient results in a larger calcium shift with increasing QT dispersion and risk of sudden death. Another possibility is that hemodialysis patients with higher serum calcium levels—who have been reported to have decreased survival compared with patients with normal serum calcium levels (7)—have increased cardiac dysfunction at baseline that puts them at risk of sudden death. It is not possible to tell with certainty which one of these factors is responsible. However, the statistical analysis from the study by Pun *et al.* (1) indicated that it was likely the gradient that was more important.

This study must also be interpreted in light of recent findings showing an increased risk of cardiac arrest during dialysis with higher dialysate bicarbonate concentrations. Alkalemia is well known to lower serum calcium, and the combination of increased alkalemia with a high calcium gradient could lead to an even higher calcium gradient and risk of sudden death.

How should this study affect our clinical care?

It is important to appreciate the complex interplay between serum calcium levels, body calcium stores, and calcium balance. Patients with normal serum calcium levels may have high, normal, or low body stores of calcium, and patients with high serum calcium levels may actually have low body stores of calcium. It would seem that management of serum calcium levels and maintenance of neutral calcium balance might use different techniques. Lower dialysate calcium concentrations seem to increase the risk of sudden death, and their use may not be preferred. Kidney Disease: Improving Global Outcomes (KDIGO) guidelines suggest a dialysate calcium concentrate of 2.5 mEq/L (8). Preferred mechanisms to lower serum calcium levels may include the use of noncalcium containing binders, cinacalcet, or vitamin

D analogs, although none of these have been found to convincingly improve survival.

What should one do about maintaining calcium balance? Recent KDIGO guidelines recommend dialysate calcium values of 2.5 mEq/L, but some nephrologists question whether lower dialysate calcium levels are needed to provide improved calcium balance (9). Fortunately, a recent study by Karohl *et al.* (10) may help to provide a solution for this dilemma. Karohl *et al.* (10) noted that calcium removal was significantly higher in patients with higher serum calcium levels and elevated serum parathyroid levels. Patients with a parathyroid level>300 pg/ml who were dialyzed with a 2.5 mEq/L calcium dialysate actually sustained a net removal of 626±487 mg calcium with each dialysis treatment.

Taken together, these results suggest that patients with higher serum calcium levels may receive adequate removal of calcium to keep overall calcium balance with a 2.5 mEq/L dialysate calcium. When serum calcium levels become elevated, we should consider other possibilities for lowering serum calcium, such as decreasing administration of calcium-based binders, decreasing use of vitamin D analogs, and perhaps, increasing use of cinacalcet. Only future studies will help us to determine if such an approach would be beneficial.

In summary, the study by Pun *et al.* (1) provides evidence of an increased risk of sudden death during hemodialysis in individuals who have a high serum-to-dialysate calcium gradient. Future studies will be needed to show us the best way to manage individuals with high serum calcium levels who are at high risk for mortality.

Disclosures

None.

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