Kidney Medicine

Individualization of Serum-to-Dialysate Potassium Concentrations to Reduce the Risk of Sudden Cardiac Death Conferred by QT-Prolonging Antibiotics in Patients Receiving Hemodialysis

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Dialysis is a life-saving procedure for patients with kidney failure, which allows for the removal of uremic retention products, other solutes, and excess fluid. The intermittent nature of hemodialysis results in a "sawtooth" pattern of fluid and solutes, and for decades, it has been appreciated that these sawtooth dynamics by no means resemble a normal physiology.[1] The availability of electronic health records has created unprecedented opportunities to analyze data from hundreds of thousands of patients and improve our understanding of patient outcomes, including exploring associations of clinical characteristics with adverse events.

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In this issue of *Kidney Medicine*, Pun et al[2] address 2 relevant yet underappreciated topics: the composition of the hemodialysate with its relationship to the prevailing serum potassium concentration and the use of antibiotic drugs that may prolong the QT interval. The authors shed light on the combined effects of the dialysate-to-serum potassium gradient and the antibiotic drugs on the risk of sudden cardiac death (SCD). Although the limitations of observational research need to be considered, it is important to reflect on what clinical implications can be gleaned from this report.

In patients receiving hemodialysis, cardiovascular disease is highly prevalent and attributed to structural and functional pathologies, such as left ventricular hypertrophy and impaired autonomous regulation. Cardiac arrhythmias, such as bradycardia, atrial fibrillation, and ventricular tachycardia, are frequent[3] and are often associated with changes in the fluid and solute levels.[4,5] Ventricular tachycardia and bradycardia[6] have been associated with SCD in patients receiving dialysis. SCD is the single most frequent cause of death in patients treated with dialysis, with incidence rate estimates varying between 4 and 7 events per 100,000 dialysis sessions.[7,8]

Although some arrhythmias are associated with structural cardiovascular abnormalities, atherosclerosis, and diabetes, arrhythmias have also been attributed to interdialytic and intradialytic changes in electrolyte concentrations[9-11] and fluid excursions.[12] Bradyarrhythmias appear most commonly toward the end of the interdialytic period, in which peak-levels of potassium are mostly noted.[3] Tachyarrhythmias occur frequently during and shortly after dialysis and are associated with rapid drops in potassium concentration and/or low potassium concentration.[3] SCD occurs most frequently toward the end of the long interdialytic interval when the highest concentrations of retention solutes and potassium and fluid overload are observed.[13]

In several publications, Assimon et al[14] have asked the question what other factors may contribute to mortality in patients treated with dialysis, and in a previous article, they reported that drugs that prolong the QT interval are a risk factor for mortality. More than 50% of the population receiving dialysis are exposed to polypharmacy, and compared with those not receiving dialysis, a large proportion of patients were prescribed at least 1 QT-prolonging medication.[14] Patients treated with dialysis frequently experience infections and, thus, infection-related hospitalizations.[15] Some infections require antibiotic therapy with drugs that may affect cardiac electrophysiology. The authors have also particularly investigated the independent association between SCD and azithromycin and fluoroquinolones, both drugs that prolong the QT interval.[16,17] In this article, an increased risk of SCD with both drugs was reported, a finding that had been corroborated in this analysis.

In their study, Pun et al[8] reported a markedly accentuated SCD risk when including the serum-to-dialysate potassium gradient as a novel effect modifier in the statistical models investigating the associations between antibiotic drug prescriptions and SCD.[18] Although the association between the risk of death and serum potassium levels was described as a U-shaped curve over the entire range of serum potassium levels,[8,18] drugs that prolonged the QT interval markedly increased the risk.

The authors used a propensity score–based inverse probability-weighting methodology, an approach that is preferred in the presence of low event counts. Although residual confounding cannot be excluded, the analysis is strengthened by a large sample size and several sensitivity analyses that also address concerns regarding potential outcome misclassifications. One shortcoming was the lack of data on the weekday when the potassium concentration was measured. However, it is unlikely that this deficit affects the conclusion of the study.

Overall, this retrospective study strongly suggests that heightened caution is warranted when prescribing drugs that prolong the QT interval in patients receiving dialysis. Repeated electrocardiograms are a sensible precaution, and seamless communication of findings between all health care professionals caring for patients receiving dialysis is

the key to reducing complications. A review of electrocardiograms before the use of drugs that may prolong the QT interval is advised to identify patients with preexisting borderline or prolonged QT-intervals. Furthermore, individualization of dialysate composition, particularly of the potassium concentration, should be considered as an approach to mitigate large dialysate-to-potassium gradients, while providing adequate treatment for hyperkalemia. Finally, care pathways that aim to mitigate the risk of SCD in patients treated with dialysis with an indication for drugs that may prolong the QT interval should be tested in sufficiently powered clinical trials.

ARTICLE INFORMATION

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