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Original Contribution

THE EFFECT OF ANTIEMETICS AND ANTIHISTAMINES ON THE QTC INTERVAL IN EMERGENT DIALYSIS PATIENTS WITH BASELINE QTC PROLONGATION

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☐ **Abstract—Background: Unfunded patients with end-stage renal disease (ESRD) who do not have routinely scheduled hemodialysis often receive medications known to prolong the QTc interval for their uremic symptoms even though they may have pre-existing QTc prolongation. Objectives: The purpose of this study was to determine the effects of these medications on the QTc interval in these patients. Methods: Unfunded patients with ESRD presenting to the emergency department (ED) for emergent hemodialysis (HD) with QTc prolongation on their initial electrocardiogram (ECG) were recruited. Approximately 2 hours after receiving an antihistamine or antiemetic, a second ECG was ordered and the QTc was measured. The patients were followed-up 1 week later. Results: Twenty-nine percent (44/152) of the unfunded patients with ESRD presenting for HD at a county hospital had QT prolongation and were included with 107 total ED visits during the 4-week study period. The mean QTc was 483.7 msec on presentation to the ED, and the mean QTc measured 2 hours after receiving an antihistamine or antiemetic was 483.8 msec. None of the patients were admitted for life-threatening dysrhythmias. Thirty-six percent (16/44) of the recruited patients had QTc intervals >500 msec with a combined total of 31 patient visits, of which only 25.8% (8/31) had an increase in the QTc interval after an antihistamine or antiemetic medication was given. None of these patients had adverse outcomes, such a dysrhythmia or death, at 1-week follow-up. Conclusion: This study shows that medications known to cause QTc prolongation are safe to use in therapeutic doses in patients with ESRD who have pre-existing QT prolongation. Few patients in this cohort had significantly prolonged QTc intervals at baseline.** © **2016 Elsevier Inc. All rights reserved.**

☐ **Keywords—antiemetics; antihistamine; dialysis; ESRD; QTc**

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INTRODUCTION

The QT interval is denoted as the time from ventricular depolarization to ventricular repolarization, with corrections (QTc) for heart rate typically being accounted for by the Bazett formula ($QTc = QT/\sqrt{RR}$). QTc prolongation is an established risk factor for sudden cardiac death caused by ventricular dysrhythmias, most frequently torsades de-pointes (1,2). In a prospective Rotterdam study by Straus et al., patients ≥55 years of age were deemed to have a 3 times greater incidence of sudden cardiac death regardless of pre-existing heart disease when they exhibited prolonged QT. In fact, they were able to show a direct correlation between sudden cardiac death risk and increasing QTc duration (1). Prolonged QT becomes a greater potential risk to patient viability when >1 coronary risk factor is present, because there is an increased incidence of sudden cardiac death to >4 times that of the general population (1).

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The prevalence of congenital QT prolongation in the general population is approximately 1 in 2500 to 5000 people, and is typically the result of autosomal dominant mutations in cardiac ion channels that convey the ability of cardiac myocytes in the ventricles to repolarize (2–4). Polymorphisms in the KCNE1 gene predispose to drug-induced prolonged QT, a pathology that is present in 2% to 3% of the population (5). Specific drugs, such as ondansetron, prolong QT by direct blockade of the human ether-a-go-go–related gene K channel. Common over the counter medications, such as diphenhydramine, an H_1 antihistamine, have dose-dependent properties that block K channels and can increase QTc intervals at significantly high doses (6,7). In a case study by Husain et al., a 44-year-old woman ingested 3 g of diphenhydramine and increased her QTc from 400 ms to 786 ms, which took 5 days to resolve (8).

One group of patients who are well known to have prolonged QTc are those afflicted with end stage renal disease (ESRD). QTc prolongation has been found to be an independent predictor of mortality in patients with ESRD (9). Once dialysis is initiated, the mean survival of patients with ESRD is 5 to 6 years, with sudden cardiac death being 10 times more likely, accounting for ≤50% of deaths (10). Voiculesco et al. studied patients with ESRD and reported that 41.2% had prolonged QTc. Interestingly, there was no correlation with sudden cardiac death or angina at 3.8 months of follow-up in these patients, but the authors found that dysrhythmias were more common after volume reduction (11).

There is a large group of patients with ESRD who reside in the United States without legal permission for residence, and they therefore lack medical funding. Many of these patients are unable to receive dialysis at outside dialysis centers and instead present to county hospitals to be dialyzed. Because of a limitation of resources and staff, these patients are dialyzed on a less frequent basis than their scheduled contemporaries in the community. These patients are dialyzed when their symptoms of overload, uremia, and electrolyte imbalances become overwhelming—or in some cases, dangerous to the patients' well-being. Medications that predispose to prolongation of the QTc are typically avoided in patients with QTc prolongation. Because of the reduced frequency of hemodialysis in our unfunded hemodialysis patients, many of them are given medications that can cause QTc prolongation to alleviate their severe uremic symptoms because no other options are available. There is currently a paucity of evidence regarding administration of QTc-prolonging medications in patients with ESRD, especially those who are not routinely dialyzed or have pre-existing prolonged QTc. Therefore, the purpose of this study is to determine the effect of antihistamines and antiemetics (which are known to cause QTc prolongation) on the QT interval in patients with ESRD and pre-existing prolonged QTc prolongation. We hypothesize that the administration of antiemetics and antihistamines in therapeutic doses does not cause significant increases in the QTc interval in patients with chronic renal failure with pre-existing QTc prolongation.

METHODS

Study Design

This study was a prospective observational study of unfunded dialysis patients who presented to a large, publicly funded county hospital for emergent hemodialysis. The study and all protocols were reviewed and approved by the institutional review board before implementation.

Study Setting and Population

This study was conducted in the emergency department (ED) of a large county hospital with an annual ED volume of >200,000 patients.

Approximately 150 unfunded hemodialysis patients present every week to this county hospital ED requesting emergent hemodialysis because their financial status does not allow them to be seen in a regular dialysis center. Only unfunded hemodialysis patients were included in this study because these were the patients who routinely presented to our ED for dialysis, were able to be consented, and were easy to follow-up because their medical care and dialysis occurred only at Parkland. Patients who have the financial resources to receive scheduled dialysis rarely present to the ED for dialysis and were not included in this study. Depending on the severity of their ESRD, there is wide variation with regard to the frequency of presentation—from as often as every 3 days to as long as twice a month. The vast majority of these patients are foreign nationals who do not qualify for financial assistance under Medicare. Their most common presenting complaints are related to volume overload and uremia, such as dyspnea, nausea, and pruritus.

The ED maintains a standard procedure for patients presenting for emergent dialysis. A complete blood cell count, electrolytes (e.g., sodium, potassium, calcium, magnesium, and phosphorus), blood urea nitrogen, creatinine, and an electrocardiogram (ECG) are obtained when the patient is brought into the treatment area. A paper copy of the ECG is delivered by hand to the senior ED resident or attending physician for immediate analysis. The hospital uses an electronic medical record (EMR) system that facilitates the recording of all laboratory orders and results, medications, ECGs, and pharmaceutical interventions. All physician orders and entries are digitally recorded and time-stamped.