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A Cautionary Tale of Combination Ceftriaxone and Lansoprazole: Should Pediatric Clinicians Heed the Warning?

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ABBREVIATIONS hERG, human ether a-go-go; ICU, intensive care unit; LQTS, long QT syndrome; PPI, proton pump inhibitor; QTc, corrected QT interval TdP, Torsades de Pointes

KEYWORDS adverse drug events; ceftriaxone; lansoprazole; pediatrics; ventricular arrhythmia

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Torsades de Pointes (TdP) is a life-threatening polymorphic ventricular arrhythmia associated with prolongation of the heart-rate corrected QT interval (QTc) as measured via electrocardiogram.[1] Prolonged QTc may result from heritable causes related to dysfunction of cardiac repolarization or it can be acquired; most acquired cases of prolonged QTc are drug related.[1] Given the potential catastrophic impact of TdP, much attention has been given to mitigating the risk of QTc prolongation in adults. Children are also vulnerable to drug-induced QTc prolongation and the risk of TdP, although the incidence is poorly defined.[2] Emerging data about drug-related QTc prolongation in adults must also be considered in the context of pediatric patient risk, particularly when the drugs are commonly used in children.

A study published in the sixth 2023 issue of *JAMA Network Open*, "Ceftriaxone and the Risk of Ventricular Arrhythmia, Cardiac Arrest, and Death Among Patients Receiving Lansoprazole," is one such example of emerging evidence with potential implications in the pediatric population.[3] Bai and colleagues[3] explored the association of adverse cardiac outcomes with a combination of ceftriaxone and lansoprazole, building on initial identification of an association with the medication combination and QTc prolongation by Lorberbaum and colleagues,[4] by using data mining and laboratory experimentation. The article by Bai et al[3] described a multicenter, retrospective cohort study evaluating adult inpatients in 13 hospitals in Ontario, Canada, during a 7-year period from 2015 to 2021. Patients were included if they were prescribed 1 or more doses of ceftriaxone during their hospital stay, and a proton pump inhibitor (PPI) at any time between the first and final dose of ceftriaxone. Patients who received lansoprazole in combination with ceftriaxone were compared with those who received any other PPI in combination with ceftriaxone. Patients were followed up until hospital discharge for a primary composite outcome of ventricular arrhythmia or cardiac arrest during the hospital stay (which did not occur prior to hospital admission), based on International Statistical Classification of Diseases and Related Health Problems, 10th Revision (ICD-10-CA) codes.[5] All-cause in-hospital mortality was a secondary outcome.

Included in the study were 31,152 patients with a mean ± SD age of 71.7 ± 16 years who were further categorized into those who received lansoprazole (n = 3747) and those prescribed other PPIs (n = 27,405).[3] Differences in baseline characteristics between the groups (e.g., age, intensive care unit [ICU] admission, and risk factors for ventricular arrhythmia) were accounted for by using adjustment based on propensity scoring. The primary composite outcome occurred in 3.4% of patients in the lansoprazole group compared with 1.2% in the other PPI group ($p < 0.001$). All-cause in-hospital mortality was also greater in the lansoprazole than in the other PPI group (19.9% vs 10.1%, respectively; $p < 0.001$). After propensity score adjustment, the adjusted risk ratios for the lansoprazole group for the composite outcome and all-cause in-hospital mortality were statistically significantly different at 2.2 (95% CI, 1.7–2.2) and 1.6 (95% CI, 1.5–1.7), respectively. The adjusted risk difference for the lansoprazole group for the composite outcome was 1.7% (95% CI, 1.1–2.3), corresponding to a number needed to harm of approximately 58. The adjusted risk difference for all-cause in-hospital mortality was 7.4% (95% CI, 6.1–8.8), corresponding to a number needed to harm of 13.

It is striking that this large, multicenter study reported increased risk for ventricular arrhythmias, cardiac arrest, and death among adults receiving the combination of ceftriaxone and lansoprazole, given the lack of attention to this combination previously. The study built upon the results of a 2016 data mining study, in which 1.6 million electrocardiogram results from 380,000 adult patients were reviewed.[4] Signals for increased

incidence of prolonged QT interval in patients receiving both ceftriaxone and lansoprazole as compared with either drug alone emerged and were validated with patch-clamp electrophysiology experiments.[4] The drug-drug interaction was not observed with PPIs other than lansoprazole. Other literature addressing this interaction is limited to a letter responding to the 2016 study by Lorberbaum and colleagues,[4] in which Lazzerini and colleagues[6] briefly describe limited experience with patients receiving the combination who subsequently experienced acquired long QT syndrome or TdP.

The proposed mechanism of the drug-drug interaction between ceftriaxone and lansoprazole resulting in prolonged QTc is an additive blockade of the human ether a-go-go (hERG) potassium channel.[4,7] A 2022 study of nearly 25,000 adults admitted to the ICU reported an association of PPIs with QT interval prolongation, with pantoprazole and lansoprazole associated with the greatest risk.[8] Less has been reported with ceftriaxone, though a retrospective pharmacovigilance study published in 2021 reported a nearly 2-fold higher odds (OR, 1.92; 95% CI, 1.8–2.05) of experiencing a cardiac disorder among ceftriaxone-receiving adults without coronavirus infection.[9]

Is this relevant in children? Should pediatric practitioners be wary of or even avoid the combination of ceftriaxone and lansoprazole in their patients? The medication combination is certainly used in pediatric patients. A point prevalence study conducted in 32 US children's hospitals determined that ceftriaxone was the second most prescribed antibiotic.[10] In another evaluation of 51 children's hospitals in 2017 and 2018, ceftriaxone was the most common antibiotic prescribed in nonsurgical patients, with 5% of medical unit patients and 9% of pediatric ICU patients receiving ceftriaxone.[11] Ceftriaxone is also frequently administered to ambulatory children in the emergency department.[12] Proton pump inhibitors such as lansoprazole are commonly used in both ambulatory and hospitalized pediatric patients.[13–15]

While no publication has specifically reported the frequency of use of both drugs in combination, internal data from the authors' local institution provide some insight. Medication usage data were queried from admissions during a 10-year period at this free-standing, academic pediatric hospital. Of the 230,212 hospital admissions from the start of 2014 through the end of 2023, a total of 335 patient admissions received at least 2 ceftriaxone doses with at least 1 lansoprazole dose in between. This equates to approximately 3 children each month who received the combination of ceftriaxone and lansoprazole. Depending on institutional formularies, patient acuity, and local prescribing patterns, this drug combination may also be commonly observed at other pediatric hospitals.

If pediatric patients do receive this drug combination, how likely is it that the findings of Bai and colleagues[3] apply to children? To date there have been no published reports of negative cardiac outcomes in pediatric patients receiving the combination of ceftriaxone and lansoprazole. Of course, absence of evidence should not imply evidence of absence. If a child had experienced prolonged QTc or TdP due to this drug combination, the interaction is unlikely to have been recognized owing to lack of evidence in children. Torsades de Pointes is rare, difficult to detect, and generally underreported. Because the incidence of drug-induced TdP is not well defined in pediatric patients, it is challenging to compare the incidence with that observed in adults.[2] Drug-induced QTc prolongation in adults is exceptionally rare in patients without predisposing risk factors.[1] It is unknown whether patient-specific factors associated with increased risk in adults, such as female sex, electrolyte abnormalities, and heart failure with reduced ejection fraction, also predispose children to drug-related TdP. Importantly, many of these underlying cardiac risk factors are rare in children, making research challenging.

Is the mechanism of this interaction likely to occur in pediatric patients? The full ontogeny of the hERG potassium channel is not well described, but evidence supports the presence of this channel from birth. Expression of the *KCNH2* gene, encoding the fast potassium channel hERG, was found to be higher in patients younger than 15 years than in adults.[16] Given that most drug-induced QT interval prolongation is due to binding to and interference with hERG potassium channels, this increased expression has been suggested as a reason why many QTc-prolonging medications may be associated with a lower impact in children than in adults.[1,17] However, QTc prolongation due to hERG-blocking medications has been reported in all age ranges of patients, including preterm infants, indicating at least some degree of risk.[17–22] Interestingly, in 1 case series, 8 of 22 patients <2 years of age who received domperidone experienced QTc prolongation, with only 2 experiencing QTc ≥450 msec. Those 2 patients were receiving concomitant lansoprazole.[21] Finally, the average age at diagnosis of long QT syndrome (LQTS) in one study was 6.8 years, with 20% of patients presenting before 1 month of age.[23] Defective hERG potassium channels, due to pathogenic *KCNH2* gene variants, cause 25% to 40% of congenital LQTS.[24] This variation, called LQTS type 2, is the second most common cause of congenital LQTS.

In conclusion, the 2023 study by Bai and colleagues[3] highlights a potentially important drug-drug interaction between ceftriaxone and lansoprazole, which may increase an adult patient's risk for ventricular arrhythmia, cardiac arrest, and in-hospital mortality. Despite the absence of evidence supporting the impact of this interaction in pediatric patients, the potential for associated negative cardiac outcomes in pediatric patients receiving the combination of ceftriaxone and lansoprazole

are concerning, given the proposed pathophysiologic mechanism of the interaction. Clinicians should consider diligent monitoring in those children receiving concomitant ceftriaxone and lansoprazole, particularly in children who are receiving other medications that may prolong QTc or in the context of electrolyte abnormalities. Use of alternative PPIs or histamine (H2) antagonists could also be considered in place of lansoprazole. Children with congenital LQTS may also be at risk and providers should consider alternative combinations, when possible. Additional research is needed to evaluate the clinical outcomes associated with this combination in the pediatric cohort.

Article Information

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