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Coupling Data Mining and Laboratory Experiments to Discover Drug Interactions Causing QT Prolongation

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ABSTRACT

BACKGROUND QT interval-prolonging drug-drug interactions (QT-DDIs) may increase the risk of life-threatening arrhythmia. Despite guidelines for testing from regulatory agencies, these interactions are usually discovered after drugs are marketed and may go undiscovered for years.

OBJECTIVES Using a combination of adverse event reports, electronic health records (EHR), and laboratory experiments, the goal of this study was to develop a data-driven pipeline for discovering QT-DDIs.

METHODS 1.8 million adverse event reports were mined for signals indicating a QT-DDI. Using 1.6 million electrocardiogram results from 380,000 patients in our institutional EHR, these putative interactions were either refuted or corroborated. In the laboratory, we used patch-clamp electrophysiology to measure the human ether-à-go-go-related gene (hERG) channel block (the primary mechanism by which drugs prolong the QT interval) to evaluate our top candidate.

RESULTS Both direct and indirect signals in the adverse event reports provided evidence that the combination of ceftriaxone (a cephalosporin antibiotic) and lansoprazole (a proton-pump inhibitor) will prolong the QT interval. In the EHR, we found that patients taking both ceftriaxone and lansoprazole had significantly longer QTc intervals (up to 12 ms in white men) and were 1.4 times more likely to have a QTc interval above 500 ms. In the laboratory, we found that, in combination and at clinically relevant concentrations, these drugs blocked the hERG channel. As a negative control, we evaluated the combination of lansoprazole and cefuroxime (another cephalosporin), which lacked evidence of an interaction in the adverse event reports. We found no significant effect of this pair in either the EHR or in the electrophysiology experiments. Class effect analyses suggested this interaction was specific to lansoprazole combined with ceftriaxone but not with other cephalosporins.

CONCLUSIONS Coupling data mining and laboratory experiments is an efficient method for identifying QT-DDIs. Combination therapy of ceftriaxone and lansoprazole is associated with increased risk of acquired long QT syndrome. (J Am Coll Cardiol 2016;68:1756–64) © 2016 by the American College of Cardiology Foundation.

Torsades de pointes is a ventricular tachycardia that can result in sudden death (1) and occurs as an adverse effect of more than 40 medications that prolong the QT interval, referred to as acquired long QT syndrome (LQTS) (2). The U.S. Food and Drug Administration (FDA) has established strict guidelines for evaluating the risk of acquired LQTS for new compounds when

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administered individually. Nonantiarrhythmic compounds that increase the QT/QTc interval by 20 ms or more are unlikely to be approved, and a compound associated with an increase of 10 ms or more would face many challenges (3). Even a 5 ms increase would prompt an evaluation of the risks and benefits of the new compound (3). Studies of both cardiac and noncardiac compounds found that a QTc interval above 500 ms is associated with significant risk of Torsades de pointes (4,5).

Acquired LQTS is of particular concern when it is not anticipated and occurs as the result of a QT interval-prolonging drug-drug interaction (QT-DDI) (2,6). QT-DDIs are not routinely evaluated preclinically and can go undiscovered for years. For example, quetiapine (an antipsychotic agent) was on the market for nearly 10 years before reports of a QT-DDI with methadone (an analgesic agent) prompted investigation into a possible mechanism (7). It took 3 more years before a label change was made to caution against the use of quetiapine in combination with other drugs known to prolong the QT interval.

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Large clinical databases, such as electronic health records (EHR), represent an opportunity to rapidly detect QT-DDIs and save lives (8,9). Drug safety algorithms could be applied to health record data in near real time, flagging potentially dangerous drug interactions before they become widespread. Furthermore, these analyses are in situ and therefore focus on the most important drug combinations: those that are actually used in clinical practice. Unfortunately, analysis of medical records is complex, due to issues of missing data, noise, and bias (10). This leads to high false positive rates and algorithms that often will mislead health care providers. Laboratory experiments, especially if they are high-throughput, can be used to screen data-mined hypotheses for plausibility. Following observational analysis with confirmatory prospective experiments can remove the spurious signals, enabling clinically useful discoveries (11).

We developed a data science pipeline to mine potential QT-DDIs from clinical databases. In this pipeline, we combine evidence of QT-DDIs from the FDA Adverse Event Reporting System (FAERS) and the EHR at New York-Presbyterian/Columbia University Medical Center (CUMC-EHR). We identified a putative interaction between lansoprazole (a proton-pump inhibitor [PPI]) and ceftriaxone (a cephalosporin antibiotic). Importantly, this is an interaction that would not have been suspected using current surveillance methods. We used patch-clamp electrophysiology of cells stably expressing human ether-à-go-go-related gene (hERG) channels to establish a physiological mechanism. We further confirmed the specificity of our pipeline by also investigating the combination of cefuroxime (another cephalosporin) and lansoprazole, a drug pair that did not have evidence of an interaction in FAERS. In the clinic, patients on the combination of ceftriaxone and lansoprazole had 12 ms (95% confidence interval [CI]: 7 to 15 ms) longer QTc intervals than patients exposed to either drug alone and were 1.4 times as likely to have a QTc interval above 500 ms. The negative control showed no significant effect. A QT-DDI between ceftriaxone and lansoprazole has the potential for significant morbidity and mortality.

ABBREVIATIONS AND ACRONYMS

APD70 = action potential duration at 70% of repolarization

DDI = drug-drug interaction

ECG = electrocardiogram

EHR = electronic health records

FAERS = Food and Drug Administration adverse event reporting system

hERG = human ether-à-go-go-related gene

LQTS = long QT syndrome

PPI = proton-pump inhibitor

QT-DDI = QT interval-prolonging drug-drug interaction

METHODS

DATA SOURCES. We used 2 independent databases to investigate possible QT-DDIs. The first database (Twosides) was a derivative of 1.8 million adverse event reports from FAERS mined for evidence of adverse drug-drug interactions that could not be explained by the individual effects of the drugs (12). The second database consisted of 1.6 million electrocardiograms (ECGs) from 382,221 patients treated at New York-Presbyterian/CUMC between 1996 and 2014. To obtain the heart rate-corrected QT (QTc) intervals, we wrote a parser to automatically extract the patient identifier, laboratory date, and QTc value from the ECG reports. QTc values were calculated using Bazett's formula. We manually checked 50 abnormal ECGs (defined as QTc >500 ms) to confirm we were extracting the correct values and found that the parser obtained 100% precision and recall. We implemented the pipeline using Python 2.7.9 (Python Foundation, Wilmington, Delaware) and R version 3.2.2. (R Foundation for Statistical Computing, Vienna, Austria).

IDENTIFICATION OF CANDIDATE QT-DDIs. We used the side effect reporting frequencies in Twosides to find drug pairs significantly over-reported with the 6 adverse events in the standardized MedDRA (Medical Dictionary for Regulatory Activities) query for "Torsade de Pointes/QT prolongation"; we call this the direct evidence model (12). However, most drug pairs are not directly reported with QT prolongation. In addition, we performed latent signal detection, a method we have previously validated (13,14), to