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Dronedarone, amiodarone and other antiarrhythmic drugs, and acute liver injuries: a case-referent study

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ABSTRACT

Background: Spontaneous reports of acute liver injuries (ALI) in patients taking dronedarone triggered an EMA alert in 2011. This study aimed to assess the risk of ALI for class III antiarrhythmic drugs controlling for the use of other potential ALI-inducing drugs.
Methods: Between 2010 and 2014, consecutive ALI cases (≥50 years-old) were identified across Germany. ALI was defined as a new increase in at least one of the transaminases ≥3 times the upper limit of normal (ULN) or ≥2 ULN if alkaline phosphatase, with ("definite" case) or without ("biochemical" case) suggestive signs/symptoms of ALI, excluding other liver diseases. Recruited community controls were matched to cases on gender, age and inclusion date. Exposure to antiarrhythmic drugs and co-medication up to 2 years before ALI onset was informed by patients and confirmed by physicians' prescriptions. Adjusted Odds Ratios (aOR) were obtained from conditional multivariable logistic regressions, adjusted for a multivariate disease risk score and co-medication.
Results: 252 cases and 1081 matched controls were included (59.1% females; mean age: 64 years). Exposure to class III antiarrhythmic drugs was 4.0% in cases and 1.5% in controls, aOR = 3.6 (95% CI: 1.6–8.4). Associations with exposure to dronedarone and amiodarone were respectively 3.1 (95% CI: 0.7–14. 8) and 5.90 (1.7–20.0). Restricting the analysis to definite or severe ALI cases did not change these results.
Conclusions: Class III antiarrhythmic drugs were associated with ALI, amiodarone displaying the highest risk, and results were robust to case definitions. Continued vigilance is needed for patients taking these drugs.

1. Introduction

Spontaneous reports of acute liver injuries (ALI) in patients using dronedarone have triggered an alert by the European Medicines Agency (EMA) in 2011 [1]. Following the alert, the EMA has recommended restricting the use of dronedarone, advising that while, drodenarone should only be prescribed after exhausting all available alternative treatment options, patients already taking this medication should have their treatment reassessed by their physician. Dronedarone is currently approved for the treatment of paroxysmal or persistent atrial fibrillation or atrial flutter, and according to the EMA's Committee for Medicinal Products for Human Use (CHMP), it should be used exclusively in these types of patients for the maintenance of sinus rhythm.

Uncertainty around the precise role of dronedarone as a risk factor for ALI with regard to other antiarrhythmic drugs and ALI-inducing co-medications in patients with atrial fibrillation justified launching specific surveillance in Germany where the drug is reimbursed and currently prescribed. The Pharmacoepidemiologic General Research eXtension (PGRx) surveillance system methodically collects cases of rare or long-latency conditions, with additional capabilities of collecting information for case-referent studies on the risk of medicines and vaccines [2–4]. The objective of this study, based on information collected through implementation of the PGRx system in Germany, was to assess the risk of ALI associated with class III antiarrhythmic drugs (potassium channel blockers), particularly dronedarone and amiodarone, controlling for other ALI associated co-medications.

2. Methods

2.1. Study population

The PGRx surveillance methodology consisted of the systematic collection of ALI cases via networks of specialized centers (case registries), also collecting a pool of referents (general practice registries) from which controls were selected and matched to cases. ALI cases and referents were recruited from across all 16 *länders* in Germany. The study population met general inclusion criteria including age 50 years and above, residence in Germany, and ability (or by proxy) to answer a questionnaire administered by telephone and to read the interview guide.

2.2. ALI cases

A network of 59 gastroenterology centers and outpatient facilities identified all new consecutive patients presenting with ALI regardless of its potential cause. Identification of ALI patients was done retrospectively for the period between September 2010 (six months after dronedarone was introduced in Germany) and February 2012, and prospectively thereafter until February 2014. Criteria for ALI included de novo elevation of liver enzymes defined as either transaminases ALT (alanine aminotransferase) or AST (aspartate aminotransferase) greater or equal to three times the upper limit of normal (ULN), or alkaline phosphatase greater or equal to two ULN and ALT or AST greater or equal to two ULN, and suggestive clinical signs and symptoms (jaundice, fatigue, nausea, vomiting, anorexia, skin eruptions, dark urine). The presence of one of the following conditions that could explain abnormalities in liver enzymes levels -viral hepatitis (except non-active carriers of hepatitis B virus), biliary obstruction, liver cirrhosis, or fibrosis- was considered an exclusion criterion. However, patients with the following conditions were eligible to participate in the study: alcoholic steatosis, acute hepatic ischemia, heart failure, acute coronary thrombosis, and severe acute hypotension. Eligible patients were classified by a panel of hepato-gastroenterologists as definite ALI cases if presenting with abnormal results for liver enzymes and suggestive clinical signs or symptoms, or as biochemical ALI cases if a classic clinical presentation was lacking. All eligible consecutive patients were offered participation in the study and a registry of eligible non-included patients was kept in order to control for a potential selection bias.

2.3. Controls

A population of "referents" was recruited by a network of 199 general practitioners (GPs) randomly selected by *länder* from a national list of GPs agreeing to participate in the PGRx program. Participation was offered to consecutive patients with no restriction as to the reasons for consultation until completing a roster of 12 volunteer patients evenly distributed by age and gender per recruiting GP. In turn, controls were randomly selected from the pool of referents without liver disease and matched to each case on gender, age (best match available within 5 years), and calendar date of inclusion (within 4 months).