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Out-of-hospital cardiac arrest

A pharmacoepidemiological approach

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Chapter 1

Introduction and outline

INTRODUCTION AND OUTLINE

Out-of-hospital cardiac arrest (OHCA) is a major public health problem that accounts for 50% of all deaths from cardiovascular causes in Western societies.[1] It is estimated that in Europe 275,000 individuals have OHCA that are attended by emergency medical services each year.[2] Most OHCAs occur at home[3,4] where treatment by emergency medical services is usually not rapidly available. Accordingly, survival rates after OHCA across Europe are 10% on average.[5] Clearly, it is desirable to identify risk factors associated with OHCA in order to elucidate the underlying mechanisms, and eventually, to prevent its occurrence.

OHCA is usually caused by cardiac arrhythmias (ventricular tachycardia [VT], ventricular fibrillation [VF]) secondary to disruptions in cardiac electrophysiology.[1] Numerous factors, often interacting, may cause such disruptions.[6] These factors include co-morbidities (coronary artery disease[1], congestive heart failure[1], diabetes mellitus[7]), genetic factors[1,8] and drug use.[9] The mechanism by which drugs possibly cause such disruption is by blocking cardiac ion channels.[9] Such block is the designed mode of action of drugs prescribed to treat cardiac diseases, in particular, Vaughan-Williams class 1 and 3 antiarrhythmic drugs. However, cardiac ion-channel blockage also occurs among drugs prescribed to treat non-cardiac disease (non-cardiac drugs).[10,11] From a clinical perspective this is important, because non-cardiac drugs constitute a broad range of widely used drugs in medical practice (antidepressants, antipsychotics, antibiotics).[12,13] Moreover, prescribers of non-cardiac drugs are likely to be non-cardiologists who may be less aware of this possible OHCA risk and/or have fewer means to monitor it. Accordingly, previous studies found increased risk of OHCA upon use of non-cardiac drugs.[14,15] Importantly, the proarrhythmic potential of these drugs was recognized after their approval into the market.[16] The best-known mechanism by which drugs increase the risk of OHCA is by blocking cardiac potassium channels, thereby prolonging the QT-interval on the electrocardiogram.[9] Prolongation of the QT-interval is considered a risk marker for the ventricular arrhythmia torsades de pointes (TdP).[9] Nowadays, it is recommended to perform an adequate premarketing investigation of the safety of new drugs that should include the assessment of QT-interval prolongation.[17]

Observational studies are a fundamental tool to study the association between drugs and OHCA risk. Hence, several OHCA cohorts have now been set up worldwide.[5,18] One example is the European Sudden Cardiac Arrest network: towards Prevention, Education and New Effective Treatment project (ESCAPE-NET project), which brought Europe's largest OHCA cohorts in one joint database.[18] The years invested in gathering data of OHCA patients allows the conduct of observational studies to explore the association between drug use and OHCA.

Repolarization blocking drugs and OHCA risk

Numerous drugs can impair cardiac repolarization by blocking cardiac potassium channels and may increase the risk of a special form of VT called TdP, which can deteriorate into VF.[9,19] Syncope, which may result from VT,[20] was first described for quinidine used in the management of atrial fibrillation.[9,19] Many years later, several publications pointed to the occurrence of QT prolongation and episodes of TdP caused by drugs used for non-cardiac conditions, such as the antihistamine terfenadine,[21] the gastrointestinal drug cisapride,[22] and the antibiotic erythromycin.[23] To increase awareness regarding drugs that cause TdP, researchers of the center for education on research and therapeutics at the University of Arizona Health Sciences Center (AZCERT) evaluated the available evidence to assess the risk of drugs to cause TdP and developed an internet-based registry to provide an up-to-date list (CredibleMeds list).[19,24,25] In this registry, drugs are classified into four risk categories based on their potential to cause TdP. [19,24,25] Category 1 drugs are defined as "drugs with a known risk of TdP even when used as recommended". Category 2 drugs are defined as "drugs that can prolong the QT-interval but there is no evidence of TdP causality, and hence are classified as having possible risk of TdP." Category 3 drugs are defined as "conditional risk of TdP and includes drugs that can increase TdP risk but only under certain conditions such as overdose, hypokalemia, bradycardia or in combination with other QT-prolonging drugs". Category 4 drugs are defined as "drugs that needs to be avoid in patients with congenital Long QT syndrome".[19,24,25] Yet, it is unknown whether these risk categories reflect OHCA risk on a population level. Filling this knowledge gap is important given the widespread use of the CredibleMeds list by prescribing physicians, patients and researchers.[24]

Depolarization blocking drugs and OHCA risk

Previous studies focusing on drug-induced arrhythmias have the limitation that they mostly focused on QT-prolonging drugs. However, emerging evidence indicates that drugs that impair cardiac depolarization and prolong the QRS interval of the ECG may increase the risk of OHCA by blocking cardiac sodium channels.[6] A link between sodium channel blocking drugs and arrhythmias was first described in the Cardiac Arrhythmia Suppression Trial (CAST).[26] This block is the designed mode of action of Vaughan-Williams class 1C cardiac antiarrhythmic drugs, but it also occurs as an off-target effect of numerous drugs prescribed to treat non-cardiac conditions, like certain antiepileptic drugs[27] and antidepressants.[6] Previous studies on depolarization blocking drugs (DB-drugs) and OHCA risk are marred by inclusion of limited number of cases,[6,27] restriction to a selected patient population,[26] or being anecdotal.[28] Studying real-world data may help to investigate whether non-cardiac DB-drugs are associated with increased OHCA risk, and whether vulnerable patient groups can be identified.

Other drug categories and OHCA

Diabetes mellitus is an important risk factor of OHCA.[7] Multiple pathophysiological changes in patients with diabetes, such as development of ischemic heart disease may increase the risk of VT/VF.[7] During myocardial ischemia cardiac ATP-regulated K-channels (K_{ATP} channels) open, leading to shortening of the action potential duration and facilitating reentrant excitation.[29] Sulfonylurea (SU) antidiabetics may block myocardial K_{ATP} channels and thereby reduce the risk of VF.[30] Previous studies focusing on SU-drugs and risk of cardiac arrest have important limitations, such as including in-hospital diagnoses to identify cardiac arrest patients[31] resulting in inclusion bias considering that most cardiac arrests occur in the community[32] or the inclusion of limited number of cases.[33] Establishing whether SU-drugs are associated with reduced OHCA risk is of great importance given the sharp rise in the prevalence of diabetes, and the increased risk of OHCA in individuals with diabetes mellitus.[7]

Previous studies showed that several drugs can influence the first registered heart rhythm during OHCA.[34,35,36] First-registered heart rhythm can be divided into shockable (VT and VF) and non-shockable rhythm (asystole, pulseless electrical activity) and is an important factor that determines survival chances after OHCA.[37] Patients with a shockable rhythm are likely to have a higher survival chance if defibrillated.[37] Previous studies found that beta-blockers may be associated with first rhythms being non-VT/VF, but these studies have yielded conflicting results.[34,35]

Outline of the thesis

The studies presented in this thesis aim to gain further insight into the role of drugs in the occurrence of OHCA risk. Data will be used from the ESCAPE-NET framework,[18] and from the Amsterdam REsuscitation STudies (ARREST) registry,[38] which is an ongoing, observational registry that includes all emergency medical services attended OHCAs in North Holland. For chapters 2-6 we also used data from PHARMO Database Network, that contains - among other things- drug-dispensing records from Dutch community pharmacies.[39] The studies in this thesis are categorized in three parts.

Part I: Repolarization blocking drugs and OHCA risk

Chapter 2 presents two independent case-control studies that investigate the OHCA risk of drugs that prolong the QT interval, either by design (cardiac QT-prolonging drugs) or as off-target effect (non-cardiac QT-prolonging drugs). Chapter 3 has a similar approach in which OHCA risk of non-cardiac QT-prolonging drugs from the two highest risk categories (category 1 ['known risk of TdP'] and 2 ['possible risk of TdP']) according to the CredibleMeds list will be studied.

Part II: Depolarization blocking drugs and OHCA risk

Chapter 4 presents a case-control study that investigates whether users of non-cardiac depolarization blocking drugs have a higher risk of OHCA compared to no users of any non-cardiac depolarization drugs. Moreover, stratified analyses according to sex and age (≤50, 50-70, or ≥70 years) is performed to identify vulnerable patient groups, and according to first-registered heart rhythm (VT/VF or non-VT/VF). Chapter 5 presents a study that investigates whether nifedipine and/or amlodipine, often-used dihydropyridines, are associated with increased OHCA risk in the general population, and how these drugs impact on cardiac electrophysiology by performing single-cell patch-clamp studies in human-induced pluripotent stem cell-derived cardiomyocytes.

Part III: Other drug categories and OHCA

Chapter 6 presents a case-control study that investigates whether use of SU-drugs (alone or in combination with metformin) is associated with decreased risk of OHCA compared to use of metformin monotherapy. Furthermore, the association of individual SU-drugs and OHCA compared to glimepiride will be investigated. Chapter 7 presents a study that investigates whether use of beta-blocker influences the first-registered heart rhythm during OHCA using OHCA registries from the Netherlands and Denmark.

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