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Review Article

Azithromycin and Cardiac Arrhythmias

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Abstract

Azithromycin is a macrolide antibiotic that is widely used for the treatment of various infections. Furthermore, it is prescribed for long periods of time in inflammatory airway or cardiovascular diseases. There have been reports of induction of cardiac arrhythmias that in some cases result to death after administration of azithromycin. Prolonged QTc-interval in the form of rectangulated potentials has been suggested to be linked to arrhythmic cardiac death in patients that had already prolonged QTc as well as in patients with no previous problems. However, attempts to study the mechanism(s) elucidating the origin of these arrhythmias, mostly implemented in animal models, did not reveal any clear arrhythmogenic substrate, making the need for further investigation more eminent. Even though azithromycin appears to be less cardiotoxic than other antibiotics, the prescription of this drug should be made under caution so as not to have the genesis of arrhythmias that could be fatal.

Keywords: Azithromycin; QTc-interval prolongation; Arrhythmias; TdP

Abbreviations

TdP: Torsades De Pointes; IKr channel: Rapidly Activating Delayed Rectifier Potassium Channel; HERG: Human Ether Related Gene; ECG: Electrocardiogram; LQTS: Long QT Syndrome

Introduction

Azithromycin represents one of the most commonly prescribed macrolide antibiotics. It is used for the treatment of various infections, mainly in the respiratory system. Azithromycin is administered in both long term and short term therapeutic approaches. For example, low-dose, long-term macrolide therapy has been reported to be very effective in patients with chronic airway diseases, such as diffuse panbronchiolitis, chronic bronchitis and bronchial asthma [1–4]. However there have been reports of deranged cardiac electrophysiologic activity in patients that have been treated with macrolide antiobiotics, including azithromycin [5]. Although the incidence of antibiotic-induced cardiac arrhythmia is relatively low, the widespread use of these drugs [6,7] exposes patients at risk to ventricular arrhythmias and represents 27.7% of drug-induced TdP polymorphic ventricular tachycardia cases reported in the literature [8].

The mechanism through which azithromycin's action is mediated is not fully elucidated *in vivo*, even though it is known that macrolide antibiotics prolong the QT interval through concentration-dependent blockade of the rapidly activating delayed rectifier potassium channel (hERG/IKr channel) [9-12]. In this review a study of the effects of azithromycin into the mechanisms of arrhythmogenesis is being attempted.

Azithromycin

Macrolides are an old class of antimicrobials with an antimicrobial spectrum against mainly Gram-positive cocci and atypical pathogens, since they can inhibit the bacterial proteinosynthesis [13]. However, there is an accumulating body of evidence over the last few years that part of the activity of macrolides is not mediated through their traditional antimicrobial effect. For example, macrolides are used in the treatment of chronic inflammatory diseases of the respiratory system due to their anti-inflammatory effect. These antibiotics are found to inhibit the release of inflammatory factors, such as IL-1β and TNFα [14,15], as well as to decrease the chronic mucus production in the airways [16,17].

Azithromycin in particular is a member of the azalides, which is a subcategory of the macrolides. Its structure is similar to erythromycin, except for the 15 atoms lactone ring. Azithromycin is widely used to treat bacterial infections, mainly in people with weak immune system, since it can connect to 50S subunit of the bacterial ribosomes, and inhibit the translation, without affecting the nucleic acids. The antibiotics antimicrobial panel is similar to that of erythromycin, including streptococci, staphylococci, mycoplasms and Chlamydia.

The lack of side effects during treatment with azithromycin is attributed to its ability to be stored in phagocytes and being transferred to the infected areas. Due to this behavior higher antibiotic concentrations are observed in tissues than in plasma. It can therefore, be administered in low dose, long term treatment [1,2,18-20]. The fact that azithromycin is believed to be one of the most effective and safe to administer among macrolides can be an explanation of its wide use. However, this macrolide has been found to affect cardiac electrophysiology, resulting to arrhythmias that in some patients can be fatal.

Cardiovascular toxicities

Cardiovascular toxicities have been one of the top-ranked causal factors, accounting for 15–34% of all drug discontinuation during development, withdrawal or causing adverse drug reactions [21,22]. Multiple medications were withdrawn from the market over the last two decades because of their association with cardiac deaths, while several other drugs were flagged for a possible association with QTc-interval prolongation. Among drugs that can cause QTc-interval prolongation are many of the prescribed antibiotics, such as macrolides. Even though primary efforts have focused on class effects

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and other quantitative structure–activity relationships, the search for predictive and translational models particularly for QTc-interval prolongation, have remained empirical [23].

Azithromycin has been reported to be relatively free of cardiotoxic effects [24]. However there are reports that this antibiotic can prolong ventricular repolarization may causing serious ventricular tachyarrhythmias including Tdp and cardiac arrest [5]. Between 2001 and 2007, case reports described arrhythmias among persons receiving azithromycin [25-29]. In 2012, Ray et al [30] reported increased risks of cardiovascular death and all-cause mortality among adult, predominantly female, Medicaid patients in Tennessee who received azithromycin compared with amoxicillin, particularly among those with a history of cardiovascular disease [31]. Subsequently, the Food and Drug Administration (FDA) and pharmaceutical manufacturer issued public safety notifications warning of QT prolongation risks with azithromycin [32].

QTc-interval prolongation

The QTc interval is the time from the beginning of the QRS complex to the end of the T wave in the surface ECG. It mainly represents the duration of ventricular repolarization. The prolongation of the ventricular myocyte repolarization is caused either by a reduction of outward currents or an increase of inward currents [33]. While congenital Long QT Syndrome (LQTS) can be precipitated by mutations producing loss of function of different K+ currents or an increase of the persistent Na+ current, virtually all drugs with QT interval prolonging potential block the rapidly activating component of cardiac delayed rectifier K+ current (IKr) [34]. IKr is rapidly activated by depolarization during the action potential and thereafter predominantly participates in rapid repolarization. IKr is carried by HERG (human ether related gene) K+ channel proteins coded by KCNH2 gene. Drugs blocking the HERG with high affinity interact primarily with the aromatic side groups of the channel, Tyr (Y652) and Phe (F656) [35]. Prolongation of the repolarization can facilitate the development of early after depolarizations mainly in M (midmyocardial) cells and Purkinje cells. Early depolarization-induced premature ventricular beats can trigger reentry and TdP especially if increased dispersion of repolarization is present.

Macrolides are among numerous and diverse medications that are most widely prescribed in the inpatient and outpatient clinical practices. In a cohort of 212,016 patients admitted to the intensive care, 2.9% of the patients received drugs known to prolong QTc interval. Azithromycin was among the top 10 of these prescriptions [5]. This antibiotic has been reported to induce TdP in patients having been diagnosed with long QT syndrome (LQTS) or other subsequent health issues also affecting the QTc-interval [11,36] as well as in patients with no risk of QTc prolongation [37]. Azithromycin has been reported to induce prolongation of repolarization in form of low-arrhythmic-risk rectangulated action potentials, compared to triangulated transformed action potentials. This effect is mediated through blockade of the rapidly activating delayed rectifier potassium channel (hERG/IKr channel), delaying the rapid phase of repoarization (Phase 3 of ventricular action potential). Channel blockade involves interactions with S6 aromatic amino acid residues of a subunits [38]. These sites are ambiguous binding sites and are not specific receptors for such antibiotics. The potency of IKr current blockers is primarily related to the affinity of drugs at the channel binding site(s) of the a-subunit of the IKr channel. The IC50 is the concentration of the drug required to produce 50% inhibition of the hERG current and can be used for the assessment of drug potency [39]. Some studies have suggested that an IC50/Cmax <10 or drug concentrations resulting in more than 10% hERG current inhibition or APD90 prolongation are associated with a clinically significant QTc prolongation [40,41]. The FDA guidance for proarrhythmic potential for nonantiarrhythmic drugs suggested that QTc prolongation <5 ms does not appear to precipitate TdP (Food and Drug Administration (US) (2004)).

However, azithromycin is a weak inhibitor of hERG current [40]. Gintant [39] showed in canine Purkinje fibers that only small increases in MAPD of less than 10% could occur at 100-fold clinical levels, compared with other antibiotics like moxifloxacin that caused 160% increases at 50-fold clinical levels. Recently azithromycin was examined for effects on temporal variability of the left ventricular MAPD (similar to alternans but at low heart rates) in the anesthetized dog with chronic AV block [40]. This animal model is highly susceptible to Tdp arrhythmia due to a lack of repolarization reserve (Iks failure) developed during chronic pacing induced remodeling. At clinically relevant intravenous doses of 2 and 8 mg/kg, azithromycin did not induce any short-term variability in repolarization of the left ventricle, and the QT, QTc and left ventricular MAPD all showed non-significant trends toward reduction. However, in the isolated rabbit heart at concentrations exceeding clinical level by more than 300-fold, whereas azithromycin did lead to increases in the QT interval and MAPD, it showed no signs of early after depolarizations (an arrhythmia triggering mechanism) or Tdp [41]. In fact, when azithromycin was combined with concentrations of erythromycin that cause Tdp in this model, arrhythmia induction was suppressed. These data together indicate that azithromycin consistently shows a lack of arrhythmic potential when used alone and when combined with other agents that prolong QT and have proarrhythmic potential. This "antiarrhythmic" effect of azithromycin might be explained by the fact that azithromycin leaves almost unchanged the rate of Phase-3 repolarization despite lengthening of action potential duration (QTc interval), namely inducing rectangulated acion potentials. Other macrolides induce triangulated action potential morphology due to excessive lengthening of Phase-3 repolarization, a potentially proarrhythmic situation specifically activating the "window" current via longterm holding of the cell membrane at depolarizing high voltage potentials.

On the other hand, retrospective studies show that azithromycin's ability to prolong QTc-interval and cause TdP, resulted in 29.8 additional cardiovascular deaths (24 due to sudden cardiac deaths) per 1 million courses of treatment, compared with amoxicillin, which is not known to affect cardiac repolarization (hazard ratio, 2.49; 95% CI, 1.38–4.50; P = 0.002) [42]. The risk of cardiac death was also significantly higher with azithromycin than ciprofloxacin (hazard ratio, 3.49; 95% CI, 1.32–9.26). More than half of these mortality cases were reported among patients in the highest decile of cardiac deaths (9.4% of the prescriptions). It was estimated that one additional death secondary to azithromycin is expected with use of 100,000 prescriptions in the low-risk group compared with 4100 prescriptions in the high-risk group. In another cohort study that involved young and middle-aged adults with a lower risk

cardiovascular death, 1,102,419 episodes of azithromycin use were compared with 7,364,292 episodes of penicillin V use. Azithromycin use was not associated with an increased risk of cardiovascular death, as compared with penicillin V (rate ratio, 1.06; 95% CI, 0.54–2.10). The upper limit of the 95% confidence interval for adjusted absolute risk difference for current azithromycin use was 11 per 1 million treatment episodes [43-45].

Concluding Remarks

The existing data exhibit the need for further investigation to better understanding the mechanisms through which azithromycin affects cardiac electrophysiology in individuals with pre-existing heart diseases, including heart failure, versus individuals without apparently cardiac diseases. Independently from current knowledge on the mechanism(s) associated with the arrhythmogenic potential of different macrolide antibiotics, the fact that experimental data do not show the induction of QTc prolongation and risk of Tdp in the same extend that clinical data exhibit, should make health practises more cautious with the prescription of azithromycin, especially in patients with a history of ventricular arrhythmias predominantly based on QTc prolongation.

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