National Essential Drug List Primary Healthcare Medication Review Process

Does azithromycin increase the risk of cardiovascular death?

Introduction

Macrolide antibiotics have been associated with cardiotoxic effects, specifically in terms of their proarrhythmic potential.[1] QT prolongation has been observed, which increases the risk of torsades de pointes[1-6] and sudden cardiac death.[7-9] Azithromycin, unlike other macrolide antibiotics, has previously not been associated with the same cardiac concerns and has a lower risk of QT prolongation.[10-11] Interestingly, azithromycin had even previously been tested for its potential for cardioprotective effects, although study results failed to reveal any benefits from its use.[12-15]

Newer concerns over the cardiac safety of azithromycin have risen, however, due to published case reports of arrhythmia-related adverse events [16-22] as well as multiple reports of torsades de pointes associated with azithromycin on the Food and Drug Administration (FDA) Adverse Event Reporting System.[23] Based on this, a cohort study was recently conducted to assess the risk of cardiovascular death with azithromycin. [24]

Literature Review

Theoretical cardioprotective effects

The role of azithromycin in cardioprotection stemmed from the concept that infections may trigger the inflammatory cascade, increasing atherosclerosis and thrombotic events.[25] *Chlamydia pneumoniae* was strongly suspected as a cause of worsening coronary artery disease (CAD), so multiple studies were undertaken to determine if treatment with azithromycin for this infection would reduce cardiovascular mortality. The ACADEMIC study [12], the AZACS study[13], the WIZARD study[14], and the ACES study[15] were all randomized controlled trials comparing azithromycin to placebo in patients with CAD, although the doses and treatment durations varied from 5 days to 1 year. In all studies, no benefit was found with the use of azithromycin for the primary endpoints, which were a composite of cardiovascular death, nonfatal myocardial infarction, recurrent ischemia, hospitalization for unstable angina, and/or coronary revascularization.

Macrolides and cardiotoxicity

Macrolides have been found to prolong the action potential duration, which is significant as QT prolongation is often used as a surrogate marker for cardiotoxicity. [1] The electrophysiologic effects of erythromycin, clarithromycin, and azithromycin have been studied, however, and were found to differ.[10] While all 3 medications had similar increases in QT interval and monophasic action potential (MAP) duration, only erythromycin and clarithromycin led to cases of early after depolarizations and torsades de pointes.

Erythromycin was previously studied in relation to its effect on sudden cardiac death.[26] A Tennessee Medicaid cohort was reviewed for confirmed sudden death from cardiac causes as well as use of concomitant cytochrome P450 (CYP) 3A inhibitors, as this would increase serum concentration of erythromycin and potentially increase the risk of cardiotoxicity. Amoxicillin use and sudden cardiac death was also evaluated. There were 1476 confirmed cases of sudden death from cardiac causes, and the multivariate adjusted rate in patients receiving erythromycin was twice as high as those who had not used any study antibiotics (incidence-rate ratio 2.01; 95% confidence interval [CI] 1.08-3.75, P=0.03). There were no significant differences among former users of erythromycin and no study antibiotic use, or between amoxicllin use and no use. The adjusted rate of sudden death from cardiac causes was significantly higher among patients taking erythromycin and concurrent CYP3A inhibitors compared to those not taking either medication (incidence-rate ratio 5.35; 95% CI 1.72-16.64, P=0.004).

Clarithromycin was studied in a randomized, placebo-controlled, multicenter trial to assess its effects on mortality and cardiovascular morbidity in patients with stable coronary heart disease.[27] The primary outcome was a composite of all-cause mortality, myocardial infarction, and unstable angina during 3 years of follow-up. The intervention was 2 weeks of clarithromycin 500 mg/day or matching placebo. Randomization resulted in 2172 patients receiving clarithromycin and 2201 receiving placebo. There were no significant effects of clarithromycin in regards to the primary outcome (hazard ratio [HR] 1.15, 95% CI 0.99-1.34). All-cause mortality, however, was significantly higher in the clarithromycin group versus placebo (HR 1.27, 95% CI 1.03-1.54, P=0.03). This was likely due to higher cardiovascular mortality with erythromycin in comparison to placebo (HR 1.45, 95% CI 1.09-1.92).

Azithromycin

A study was published by Ray and colleagues regarding the issue of azithromycin and risk of cardiovascular death.[24] This cohort study reviewed a group of Tennessee Medicaid patients, which included 347,795 prescriptions for azithromycin between 1992 and 2006.[24] Patients with azithromycin prescriptions were compared to a control group of 1,391,672 patients with no prescriptions for antibiotics, a group of 1,348,672 patients with amoxicillin prescriptions, a group of 264,626 patients with ciprofloxacin prescriptions, and a group of 193,906 patients with prescriptions for levofloxacin. Patients were between the ages of 30 and 74 years and were excluded if they were considered at high risk for death from causes unrelated to a short-term exposure to a proarrhythmic medication. Additionally, patients could not have resided in a nursing home in the last year or been

hospitalized in the last 30 days. The lower limit of 30 years of age was set by the authors as sudden death in children and young adults is rare.
The primary endpoints of the study were cardiovascular death and death from any cause.[24] Cardiovascular deaths were identified by a computerized death certificate file and had to have an underlying cause of death consistent with a cardiovascular disease based on International Classification of Diseases (ICD-9) codes. An additional outcome included sudden cardiac death, which was defined as "a sudden pulseless condition that was fatal, consistent with aventricular tachyarrhythmia, and occurred in the absence of a known noncardiac condition as the proximate cause of the death." Study comparisons were all adjusted for a large set of covariates that could have been associated with both the use of an antibiotic as well as the risk of death. Propensity scores were used for each matched comparison.

There were no major significant differences between groups.[24] Among patients with prescriptions for azithromycin, there were 29 cardiovascular deaths during the 5-day treatment course or 85.2 per 1 million courses.[24] Additionally, 22 of these deaths were considered sudden cardiac deaths (64.6 per 1 million courses). In comparison, patients with no antibiotics during a same 5-day period had 41 cardiovascular deaths (29.8 per 1 million courses) and 33 sudden cardiac deaths (24.0 per 1 million courses). During the first 5 days of treatment of amoxicillin, there were 42 cardiovascular deaths (31.5 per 1 million courses) and 29 sudden cardiac deaths (21.8 per 1 million courses). The risk for cardiovascular death for azithromycin compared to no antibiotic was increased (HR 2.88, 95% CI 1.79-4.63, P<0.001) during days 1 to 5. The risk of death from any cause was also increased with azithromycin (HR 1.85, 95% CI 1.25-2.75, P=0.002) for days 1 to 5, but this risk became non-significant when looking at the entire 10-day period after the prescription was filled (HR 1.27, 95% CI 0.92-1.75, P=0.20). In comparison, amoxicillin was not associated with an increased risk of death from cardiovascular or noncardiovascular causes at 5 or 10 days versus no antibiotics. Similar results were found when azithromycin was compared to amoxicillin. There were statistically significant increased risks of cardiovascular death at 5 and 10 days (HR 2.49, 95% CI 1.38-4.50, P=0.002 and HR 1.87, 95% CI 1.16-3.01, P=0.01, respectively) with azithromycin, but only a statistically significant risk of death from any cause at 5 days (HR 2.02, 95% CI 1.24-3.30, P=0.005). In comparison to ciprofloxacin, azithromycin was found to have an increased risk of cardiovascular death at 5 days (HR 3.49, 95% CI 1.32-9.26, P=0.01) but not for death from any cause. There was no statistically significant difference between azithromycin and levofloxacin for cardiovascular death or for death from any cause.

Summary
Azithromycin has historically been considered safer than other macrolides in regards to cardiotoxicity and proarrhythmic potential.[10-11] It has even been studied previously for its potential for cardioprotection by eradicating *C pneumoniae*, which was thought to have atherogenic properties. [12-15,25] More recently, however, newer case reports and reporting by the FDA have prompted concern about azithromycin and its potential to cause arrhythmias, torsades de pointes, and sudden cardiac death.[16-23] Based on this, a cohort study was performed to evaluate the association between azithromycin use and cardiovascular death.[24] While this study did not compare azithromycin to other macrolides, it did compare azithromycin to patients with no antibiotics, amoxicillin, ciprofloxacin, and levofloxacin. There was a statistically significant increase in cardiovascular death as well as death from any cause when looking at azithromycin in comparison to no antibiotics as well as amoxicillin. Only cardiovascular death was significantly increased in comparison to ciprofloxacin, and there was no significant difference in comparison to levofloxacin.

This study suggests that there are evidence-based concerns for cardiotoxicity with azithromycin and that the idea that azithromycin is essentially safe in regards to cardiac events is no longer valid. As this study did not compare azithromycin to other agents in its class and previous studies have shown reduced cardiotoxicity in comparison to erythromycin and clarithromycin, it is still appropriate to use this agent for accepted indications. The incidence of cardiovascular death was still relatively small with azithromycin (85.2 per 1 million treatment courses), thus routine use of cardiac monitoring during treatment with azithromycin in the general population is not warranted at this time. Based on the available evidence, consideration for the use of azithromycin with other agents that may have proarrhythmic effects or in patients with underlying cardiovascular diseases should be part of the clinical discussion when determining an appropriate treatment plan, and appropriate monitoring should be considered in high-risk patients.

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