The cardiovascular safety of azithromycin

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Azithromycin is one of the most widely used antibiotics in clinical practice. More than 50 million prescriptions are issued in the United States annually, typically for respiratory tract and sexually transmitted infections. The drug has become popular because of its broad spectrum of antimicrobial activity, convenience of dosing and favourable drug interaction profile relative to its predecessors erythromycin and clarithromycin.[1] It has also been considered relatively safe; however, in 2012, a widely publicized study raised concerns about its cardiovascular safety. Subsequent studies suggested these concerns may have been overstated.

In 2012, the *New England Journal of Medicine* (*NEJM*) published a study involving the health records of Medicaid recipients in Tennessee.[2] The study found that azithromycin was associated with an increased risk of cardiovascular death relative to amoxicillin (odds ratio 2.49, 95% confidence interval [CI] 1.38–4.50).[2] The publication spawned extensive media coverage, with headlines that grew even more disquieting following a review of the available data by the US Food and Drug Administration (FDA).

A year later, *NEJM* published a study from Denmark involving 1.1 million treatment courses of azithromycin, which found no increased risk of cardiovascular death relative to penicillin V (rate ratio 0.93, 95% CI 0.56–1.55).[3] This study garnered considerably fewer headlines, but was accompanied by a commentary from officials at the FDA,[4] which had only a few months earlier strengthened its warnings about the cardiac risk of azithromycin.[5] The authors argued that the new study did not exclude an increased cardiovascular risk because it involved patients who were relatively healthy.[4]

The 2012 study was predicated on the observation that azithromycin can prolong the QT interval.[2] A prolonged QT interval is a major risk factor for torsades de pointes, the same potentially lethal arrhythmia responsible for the disappearance from pharmacy shelves of terfenadine, cisapride, astemizole and grepafloxacin. Although azithromycin can cause QT prolongation,[6] it does so to a lesser extent than either erythromycin or clarithromycin.[7,8] Moreover, despite the widespread use of azithromycin, reports of torsades de pointes in patients taking this drug are exceedingly rare, and almost all of them involve patients with other risk factors for QT prolongation.[6] Consequently, the role of azithromycin in each case is unclear. In a meta-analysis of six randomized trials comparing azithromycin with placebo in almost 14 000 patients with established coronary disease — an inherently high-risk group — azithromycin was associated with a trend toward reduced mortality (odds ratio 0.91, 95% CI 0.77–1.09).[9] Finally, a recent observational study involving more than 70 000 adults admitted to hospital with pneumonia found that treatment with azithromycin was associated with lower 90-day mortality and no increase in arrhythmias.[10] From these observations, it is tempting to speculate that azithromycin may not be as dangerous as the initial headlines suggested.

The two studies published in *NEJM* most likely reached different conclusions because they involved patients with different characteristics.[2,3] In the first study, azithromycin recipients were on average nine years older (49 v. 40 yr) and much more likely to have received β-adrenergic blockers (21.5% v. 4.7%), angiotensin-converting enzyme inhibitors (28.1% v. 6.0%), loop diuretics (17.2% v. 2.4%) and statins (28.0% v. 4.1%). In other words, cardiac risk related to azithromycin appears limited to patients with greater medical complexity.

Key points

- Recent studies have yielded conflicting information about the cardiovascular safety of azithromycin.
- The association between azithromycin and cardiovascular death most likely represents the effects of infection rather than a direct effect of the drug.
- Although azithromycin can influence cardiac conduction, adverse consequences are largely confined to patients with established cardiac disease.
- Caution is warranted when prescribing azithromycin to patients with pre-existing QT prolongation or risk factors for it, including hypokalemia, hypomagnesemia and use of other QT-prolonging drugs.

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The clinically important question, however, is whether azithromycin itself causes cardiovascular death or is simply a marker of increased risk. Patients who are sick enough to warrant broad-spectrum antibiotics sometimes die, particularly when burdened with comorbidities. To enhance inferences regarding causality of the association between azithromycin and risk of cardiovascular death, the 2012 study employed a variety of approaches, including a comparison with amoxicillin.[2] The problem here is obvious: amoxicillin and azithromycin are prescribed for very different indications. This was borne out in the study; 45% of azithromycin recipients with a documented indication for treatment had an infection of the lower respiratory tract, compared with only 27% of amoxicillin recipients. Moreover, azithromycin was not associated with an increased risk of cardiovascular death relative to levofloxacin, a more clinically appropriate comparator, albeit one that itself can sometimes cause QT prolongation.

The authors also explored azithromycin's safety as a function of baseline cardiovascular risk and found the strongest "signal" in patients with the highest baseline risk. This too is not surprising, because the patients least able to tolerate a serious infection (of the lower respiratory tract in particular) are those with severe cardiovascular disease. It is therefore likely that many, if not most, cases of sudden death during azithromycin therapy were the result of infections in medically frail patients, rather than the direct effect of the drug itself.

Relative risk estimates can be misleading, particularly when applied to rare but serious events. Because clinicians generally prefer to think in numbers rather than rates, what matters most when making clinical decisions is the absolute risk (or benefit) of an intervention, rather than relative estimates. In both studies,[2,3] fewer than 100 deaths occurred per million prescriptions for azithromycin. For contextual purposes, let us assume that half of all sudden deaths in the 2012 study were directly caused by azithromycin — an implausibly high proportion. A physician caring for similar patients would need to issue 20 azithromycin prescriptions every working day for about six years to trigger one arrhythmic death.

Physicians should not be reluctant to prescribe azithromycin when a valid indication is present. For most patients, the absolute risk of a serious arrhythmia is infinitesimal. However, because the drug does carry risk, it remains prudent to prescribe azithromycin cautiously, particularly in patients susceptible to arrhythmia, such as those with baseline QT prolongation, hypokalemia or hypomagnesemia, as well as those taking sotalol, methadone or other drugs with similar effects on repolarization.[11] Even in these patients, however, treatment with a macrolide will occasionally be unavoidable. In such instances, the safest course of action is to correct reversible causes of QT prolongation while limiting the dose and duration of antibiotic therapy. In patients who have an especially high risk of arrhythmia, periodic monitoring with electrocardiography during therapy offers an additional measure of safety.

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