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Medicines Evidence Commentary

commentary on important new evidence from Medicines Awareness Weekly

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Azithromycin and cardiovascular risk

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An observational study in the USA suggests that, compared with amoxicillin or no antibiotic treatment, a 5-day course of azithromycin was associated with a small absolute increase in the risk of death, particularly in people who were at a higher risk of cardiovascular disease. The volume of prescribing of azithromycin in the UK means that if these results were confirmed, the population risk is limited. Regulators have assessed the new data and the product information is currently being updated to strengthen the existing precautions in the azithromycin summaries of product characteristics (SmPCs). For most common primary care infections, Public Health England recommend a number of other antibiotics rather than azithromycin. Clinicians considering prescribing azithromycin in primary care should ensure this is in line with that guidance, is appropriate for that individual, and that their prescribing has taken into consideration the cautions for QT prolongation in the azithromycin SmPCs.

Overview and current advice

Management of infection guidance for primary care for consultation and local adaptation[1], published by Public Health England in February 2013 recommends azithromycin as a first-line option only in Chlamydia trachomatis. A single 1 gram dose should be used for chlamydial urethritis or uncomplicated genital chlamydial infection.

More information on azithromycin and other macrolides can be found in the British National Formulary (BNF), the BNF for Children and the relevant summaries of product characteristics. The BNF states that macrolides should be used with caution in people with a predisposition to QT interval prolongation (including electrolyte disturbances and concomitant use of drugs that prolong the QT interval).

Recent observational studies looking at longer treatment durations than a single dose have raised the possibility that azithromycin may increase the risk of cardiovascular death[2,3]. This medicines evidence commentary focusses on a study which suggests an association between azithromycin use and increased risk of cardiovascular death compared with amoxicillin or no antibiotic treatment (Ray WA et al 2012[2]).

New evidence

The study by Ray WA et al (2012)[2] was a retrospective cohort design that compared the risk of death in people aged 30 to 74 years (mean age 49 years) who were enrolled in the Tennessee Medicaid program and took azithromycin, other selected antibiotics, or no antibiotics between 1992 and 2006. The primary endpoints were cardiovascular death and death from any cause.

During 5 days of therapy, azithromycin was associated with an increased risk of cardiovascular death (hazard ratio [HR] 2.88, 95% confidence interval [CI] 1.79 to 4.63, p<0.001) and death from any cause (HR 1.85, 95% CI 1.25 to 2.75, p=0.002), compared with no antibiotic treatment. There was no association between azithromycin and death from noncardiovascular causes. People who took amoxicillin had no increased risk of death, compared with no antibiotic treatment. This study did not assess the safety of a single dose of azithromycin.

Compared with amoxicillin, azithromycin was associated with an increased risk of cardiovascular death (HR 2.49, 95% CI 1.38 to 4.50, p=0.002) and death from any cause (HR 2.02, 95% CI 1.24 to 3.30, p=0.005) over 5 days of therapy. The risk of cardiovascular death was significantly greater with azithromycin than with ciprofloxacin (HR 3.49, 95% CI 1.32 to 9.26, p=0.01) but did not differ significantly from that with levofloxacin.

Although the authors addressed potential confounding factors, the study results should nevertheless be interpreted with some caution because of residual uncertainty about confounding factors. These may include existing cardiovascular disease and other coexisting conditions, risk factors associated with cardiovascular disease (such as smoking, high body mass index, poor diet and low physical activity) and the indication for antibiotic therapy.

A later study by Svanström H et al (2013)[3] has found that azithromycin was not associated with an increased risk of death from cardiovascular causes. However, the Danish population in this study was younger (mean age around 40 years) and had a lower baseline risk of cardiovascular disease and death than that in Ray WA et al (2012)[2]. Svanström H et al (2013)[3] suggest that the risk of cardiovascular death with azithromycin might be limited to people at a high baseline risk of cardiovascular disease.

Commentary

The study was undertaken in the USA where azithromycin usage may be different from the UK. The most common indications for azithromycin in Ray WA et al (2012)[2] were infections of the ear, nose, or throat and bronchitis. Azithromycin is licensed for a wide range of infections including those of the respiratory tract, otitis media and soft tissues but Public Health England's Management of infection guidance recommends it only for single dose, first line use for treatment of Chlamydia trachomatis infections.

The absolute increase in the risk of cardiovascular death seen in this study with a 5-day course of azithromycin compared to amoxicillin was small with 47 additional deaths per 1 million courses. The excess risk over amoxicillin varied according to baseline cardiovascular risk; this was calculated using de novo propensity scoring. There was around 1 excess cardiovascular death per 4100 prescriptions in people with the highest cardiovascular risk and less than 1 per 100,000 in people with the lowest cardiovascular risk.

In the year ending March 2013, approximately 418,000 prescriptions for azithromycin were dispensed in primary care in England, and 86% of these were not for the single dose

treatment recommended by the Management of infection guidance for chlamydia infections (NHS Business Services Authority Prescription Services; personal communication). Applying the results of Ray WA et al (2012)[2], and assuming the baseline cardiovascular risk of UK patients prescribed azithromycin is the same as the patients in the study cohort, and the absolute risk increase from azithromycin compared with amoxicillin seen in the study is accurate and does not apply to single dose usage, the absolute increase in cardiovascular deaths per year in England associated with azithromycin would be 17.

The summary of product characteristics for azithromycin (Zithromax)[4] already states that other macrolides may prolong cardiac repolarisation and QT interval, and that it cannot be excluded that azithromycin may also carry a risk of cardiac arrhythmia and torsades de pointes in patients at increased risk for prolonged cardiac repolarisation. In light of the emerging data specific to azithromycin, regulators are now in the process of strengthening this existing precaution around use of azithromycin in patients with risk factors for ventricular arrhythmias (including torsade de pointes).

The summaries of product characteristics for clarithromycin and quinolones contain similar cautions. When any of these antibiotics are prescribed, the potential consequences of QT interval prolongation should be considered, particularly in people with cardiovascular risk factors.

Careful decision making early in the course of a non-specific respiratory infection regarding which patients need antibiotics, and then which antibiotic to prescribe continues to be important. In some conditions and in some patients, antibiotics have only limited benefits and other management options may be considered.

For most common primary care infections the Public Health England guidance recommends a number of other antbiotics rather than azithromycin. Clinicians considering prescribing azithromycin in primary care should first ensure that this choice is in line with those recommendations and is appropriate for that individual. If azithromycin is still considered the appropriate choice, and the patient does not have any increased risks for QT prolongation as outlined in the SmPCs, and does have significantly raised risks of complications from their infection, the iatrogenic risk is likely to be outweighed several times over by the estimated risk reduction in death from infection complications achieved by the antibiotic prescribing.

See the NICE clinical guideline on respiratory tract infections, the NICE pathway on self-limiting respiratory tract infections – antibiotic prescribing and the QIPP key therapeutics topic on antibiotic prescribing. See the NICE Evidence topic page on antibacterials for a general overview of this area.

Study sponsorship

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References

1. [Add text. Health Protection Agency (February 2013) Management of infection guidance for primary care for consultation and local adaptation
2. Ray WA, Murray KT, Hall K, et al. (2012) Azithromycin and the risk of cardiovascular death. N Engl J Med 366: 1881–90
3. Svanström H, Pasternak B, Hviid A. (2013) Use of azithromycin and death from cardiovascular causes. N Engl J Med 368: 1704–12

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