ARTICLE

Prescribing azithromycin

SUMMARY

Azithromycin is a broad-spectrum macrolide antibiotic with a long half-life and excellent tissue penetration.

It is primarily used for the treatment of respiratory, enteric and genitourinary infections and may be used in preference to other macrolides for some sexually transmitted and enteric infections.

Azithromycin has additional immunomodulatory effects and has been used in chronic respiratory inflammatory diseases for this purpose.

Potential major adverse effects include cardiovascular arrhythmias and hearing loss. Macrolide resistance is also a problem, as are interactions with commonly prescribed drugs.

Brendan J McMullan
Staff specialist
Infectious diseases

Mona Mostaghim
Antimicrobial stewardship and quality use of medicines pharmacist

Sydney Children's Hospital

Key words
antibiotic resistance, azithromycin, immunomodulators, macrolide antibiotics

Aust Prescr 2015;38:87–9

Introduction

Azithromycin is a broad-spectrum macrolide antibiotic with bacteriostatic activity against many Gram-positive and Gram-negative bacteria including *Bordetella pertussis* and *Legionella* species. It also has activity against *Mycoplasma pneumoniae*, *Treponema pallidum*, *Chlamydia* species and *Mycobacterium avium* complex.[1]

Since the late 1990s, macrolide-resistant *Streptococcus pneumoniae* and *Staphylococcus aureus* infections have been increasing in Australia. Over 10% of *S. pneumoniae* infections and over 15% of *S. aureus* infections have been reported to be resistant to azithromycin.[2,3] *Haemophilus influenzae* is commonly susceptible to macrolides but resistance rates of 3–15% have been reported in Aboriginal and Torres Strait Islander children.[4]

Pharmacology

Azithromycin reversibly binds to the bacterial ribosome and inhibits protein synthesis.[5,6] The drug has an absolute oral bioavailability of 35–42% in healthy volunteers and people with cystic fibrosis[7,8] and a long half-life due to extensive uptake in tissue, particularly lung, tonsil and prostate. Tissue concentrations exceed the minimum inhibitory concentration that would inhibit 90% of likely pathogens (MIC90) after a single 500 mg oral dose. Mean concentrations in tissue are 10–100-fold higher than those reached in serum and persist for several days.[1] Azithromycin also accumulates in phagocytes, with levels up to 200 times greater than in serum,[1] but penetrates poorly into cerebrospinal fluid and peritoneal fluid.

Azithromycin is generally administered orally, but an intravenous formulation exists for patients unable to tolerate oral medications. Duration of treatment varies with indication and severity. Usually a single dose is recommended in some sexually transmitted infections. Several days of treatment is generally appropriate in respiratory tract infections and many months in mycobacterial infections. Guidelines should be consulted for detailed recommendations.[9]

Unlike clarithromycin, azithromycin does not interact significantly with cytochrome P450 3A4.[1] In comparison with erythromycin, it is more acid stable, which simplifies administration around food.

Azithromycin is a pregnancy category B1 drug and is considered safe to use in pregnancy and breastfeeding. However, it may cause diarrhoea in breastfeeding infants.[9,10]

Indications

In Australia, azithromycin is subsidised by the Pharmaceutical Benefits Scheme (PBS) for a number of indications (see Table). It is also recommended for other infections by guidelines, but not specifically approved by the Therapeutic Goods Administration. Infections that may be treated with azithromycin include:

- community-acquired pneumonia
- specific respiratory infections, including pertussis and legionellosis
- sexually transmitted infections such as orchitis, pelvic inflammatory disease, chancroid and granuloma inguinale[9]
- bacterial enteritis due to *Campylobacter* and *Salmonella* species, cholera and travellers' diarrhoea, as well as enteric fever (caused by *Salmonella enterica* serovar Typhi and *S. enterica* serovar Paratyphi).

Other recommended uses of azithromycin include treatment of severe infection or persistent lymphadenopathy due to *Bartonella henselae* (cat-scratch disease), and some tick-borne infections such

Table **Pharmaceutical Benefits Scheme indications for azithromycin**

Schedule	Drug	Restriction	Repeats
General schedule	azithromycin 500 mg tablets (2/pack)	trachoma	2
		uncomplicated urethritis or cervicitis due to *Chlamydia trachomatis*	0
General schedule	azithromycin 200 mg/5 mL oral liquid (powder for 15 mL)	trachoma	0
Repatriation schedule	azithromycin 500 mg tablets (3/pack)	upper and lower respiratory tract infections	0
Highly specialised drugs (Section 100)	azithromycin 600 mg tablets (8/pack)	prevention of *Mycobacterium avium* complex in patients with HIV (CD4 counts <75/mm^3)	5

Based on www.pbs.gov.au [cited 2015 May 5].

as Australian tick typhus or scrub typhus. It is also used as part of combination therapy for *M. avium* complex infections.[9]

Azithromycin as an immunomodulator

In addition to their antimicrobial properties, there are in vitro and animal data on the immunomodulatory or anti-inflammatory effects of macrolides.[1] Effects in humans were initially reported in the treatment of diffuse panbronchiolitis, in which macrolides are associated with improved lung function and prognosis based largely on non-controlled trial data and retrospective studies.[1] In cystic fibrosis, treatment for six months is associated with improved respiratory function and reduced respiratory exacerbations.[11] Azithromycin produced a small increase in lung function (mean 8.8%) at seven months in patients treated for bronchiolitis obliterans syndrome after lung transplant,[12] but was no different compared to placebo for bronchiolitis obliterans syndrome after haematopoetic stem cell transplant.[13]

Azithromycin and other macrolides have also been proposed for use in sepsis and epidemic respiratory viral infections to prevent cytokine storm.[1] It has been used for various respiratory and non-respiratory inflammatory conditions. However, this use has been controversial due to limited direct clinical evidence for many conditions, and concerns about increased antimicrobial resistance.[1,14] New non-antibiotic macrolides may provide immunomodulatory benefits without contributing to antimicrobial resistance.[14]

Bronchiectasis

In non-cystic fibrosis bronchiectasis, three randomised, double-blind, placebo-controlled trials found that azithromycin reduced the number of exacerbations. In adults with bronchiectasis on CT scanning and at least one pulmonary exacerbation treated with antibiotics in the past year, the EMBRACE trial found a reduction in the rate of exacerbations (0.59 vs 1.57) with azithromycin three times weekly for six months compared to placebo.[15] The BAT trial found a reduced number of exacerbations (median 0 vs 2) in adults with radiologically confirmed bronchiectasis and at least three respiratory infections treated with antibiotics in the past year (daily azithromycin therapy over 12 months).[16] Finally, the Bronchiectasis Intervention Study investigated Australian and New Zealand indigenous children with non-cystic fibrosis bronchiectasis or chronic suppurative lung disease who had had at least one pulmonary exacerbation in the past 12 months. After once-weekly azithromycin for up to 24 months, the incidence of pulmonary exacerbations was half that observed in those given placebo. However, the authors noted a greater incidence of macrolide-resistant bacteria in children treated with azithromycin (46% vs 11%).[17]

Asthma and chronic obstructive pulmonary disease

Trials in children and adults with asthma and chronic obstructive pulmonary disease (COPD) have been small with heterogeneous outcomes, and the optimal regimens and subgroups are not yet established. Patients with neutrophilic asthma may benefit from macrolides, but further research is needed.[18]

A randomised controlled trial of daily azithromycin in patients with variable COPD severity, smoking status and medical management found that azithromycin prolonged time to exacerbation compared to placebo – median 266 days (95% CI* 227–313) versus 174 days (95% CI 143–215) (p<0.001). The rate of exacerbations was 1.48 per patient-year in the azithromycin group, compared with 1.83 in the placebo group (p=0.01). However, there was only a 7% increase in the proportion of people reporting clinically important improvements

* CI confidence interval

in quality of life with azithromycin as compared with placebo (43% vs 36%, p=0.03). Patients in the azithromycin arm experienced hearing decrements more frequently (25% vs 20%, p=0.04) and were more likely to be colonised with macrolide-resistant organisms (81% vs 41%, p<0.001). People with a prolonged QT interval were excluded from this study.[19]

Adverse effects

Azithromycin is generally well tolerated, but relatively common adverse effects (1–5% of patients) include gastrointestinal upset, headache and dizziness. Transient increases in transaminases have also been reported in 1.5% of patients.[5]

Hearing loss or impairment has also been reported with azithromycin, including in patients with COPD and normal hearing at baseline, and appeared to be irreversible in some patients.[19,20] Case reports of hearing loss after short-term use have also been published.[21]

Serious adverse effects include QT prolongation and torsades de pointes resulting in death. The US Food and Drug Administration issued a warning in 2012 to consider the risk of fatal heart rhythms in those:

- with a prolonged QT interval (including congenital long QT syndrome)
- taking medicines that are likely to prolong the QT interval
- with a history of torsades de pointes, arrhythmias or uncompensated heart failure.

This advice was primarily based on a large retrospective cohort study that suggested an increase in cardiovascular deaths, and death from any cause, in people treated with a five-day course of azithromycin compared to amoxycillin, ciprofloxacin, or no drug.[22]

At an individual and a population level, macrolides have been associated with antibiotic resistance in *Streptococcus pneumoniae* and *S. pyogenes*, *Staphylococcus aureus*, *Haemophilus* species and other organisms.[1,14] Patients with chronic lung diseases treated with long-term azithromycin had a 2.7-fold increased risk of macrolide-resistant bacteria, according to a recent meta-analysis.[20] This has potential adverse clinical consequences for the individual and the community.

Clinically significant drug interactions

Azithromycin has a number of clinically relevant drug interactions (see Box).[23-29] Due to its long half-life, interactions may continue for several days after it has been stopped.[10]

When is azithromycin preferable to other macrolides?

While there is no clear advantage of azithromycin over other macrolides for most respiratory infections, its pharmacokinetic properties make it useful for treatment of sexually transmitted infections (e.g. single-dose azithromycin for urethritis with *Chlamydia trachomatis*).[9] In addition, its high intracellular concentrations and high potency in vitro are proffered as reasons for use against enteric pathogens such as *Salmonella* species (which are intrinsically resistant to erythromycin due to active efflux). Azithromycin's once-daily dosing for the prevention and treatment of *M. avium* complex and its lack of interactions via cytochrome P450 may make it preferable to clarithromycin in some circumstances.

Conclusion

Azithromycin's pharmacokinetics and tolerability make it particularly useful in the treatment of sexually transmitted infections, intracellular enteric pathogens and for prophylaxis of mycobacterial disease. It is also useful for treating a range of respiratory diseases. Unfettered use of azithromycin, particularly for its immunomodulatory properties, is of concern in light of macrolide resistance. Novel non-antibiotic macrolides may be used for this role in future. ◁

Conflict of interest: none declared

Box Clinically significant interactions of azithromycin

- Azithromycin should be used with great caution if co-administered with other drugs that prolong the QT interval.[23]
- There are a number of published reports suggesting that azithromycin might potentiate the activity of warfarin, however clinical events due to excessive anticoagulation attributable to warfarin are controversial due to patient factors and study design. Some retrospective series have failed to find interactions[24,25] or found an interaction but no adverse events.[26] Given the current uncertainty about interactions, it is prudent to monitor INR carefully in patients on warfarin who require azithromycin.
- Pharmacokinetic modelling suggests reduced clearance of everolimus.[27]
- Macrolides, including azithromycin, may potentiate digoxin toxicity. This relates to P-glycoprotein. A case report describes a 31-month-old who developed symptoms of digoxin toxicity after starting azithromycin.[28]
- Azithromycin may increase colchicine concentrations, with consequent toxicity.[10,27]
- Concomitant use of statins and azithromycin may increase the risk of rhabdomyolysis.[29]
- Co-ingestion of antacids (aluminium, magnesium) may reduce the peak concentration of azithromycin.

REFERENCES

1. Parnham MJ, Erakovic Haber V, Giamarellos-Bourboulis EJ, Perletti G, Verleden GM, Vos R. Azithromycin: mechanisms of action and their relevance for clinical applications. Pharmacol Ther 2014;143:225-45.
2. Nimmo GR, Pearson JC, Collignon PJ, Christiansen KJ, Coombs GW, Bell JM, et al. Antimicrobial susceptibility of *Staphylococcus aureus* isolated from hospital inpatients, 2009: report from the Australian Group on Antimicrobial Resistance. Commun Dis Intell 2011;35:237-43.
3. Gottlieb T, Collignon P, Robson J, Pearson J, Bell J. *Streptococcus pneumoniae* survey. 2007 Antimicrobial Susceptibility Report. Australian Group on Antimicrobial Resistance; 2009.
4. Hare KM, Singleton RJ, Grimwood K, Valery PC, Cheng AC, Morris PS, et al. Longitudinal nasopharyngeal carriage and antibiotic resistance of respiratory bacteria in indigenous Australian and Alaska native children with bronchiectasis. PLoS One 2013;8:e70478.
5. Zuckerman JM, Qamar F, Bono BR. Macrolides, ketolides, and glycylcyclines: azithromycin, clarithromycin, telithromycin, tigecycline. Infect Dis Clin North Am 2009;23:997-1026, ix-x.
6. Hansen JL, Ippolito JA, Ban N, Nissen P, Moore PB, Steitz TA. The structures of four macrolide antibiotics bound to the large ribosomal subunit. Mol Cell 2002;10:117-28.
7. Beringer P, Huynh KM, Kriengkauykiat J, Bi L, Hoem N, Louie S, et al. Absolute bioavailability and intracellular pharmacokinetics of azithromycin in patients with cystic fibrosis. Antimicrob Agents Chemother 2005;49:5013-7.
8. Foulds G, Shepard RM, Johnson RB. The pharmacokinetics of azithromycin in human serum and tissues. J Antimicrob Chemother 1990;25 Suppl A:73-82.
9. Antibiotic Expert Groups. Therapeutic guidelines: antibiotic. Version 15. Melbourne: Therapeutic Guidelines Limited; 2014.
10. Australian Medicines Handbook. Adelaide: Australian Medicines Handbook Pty Ltd; 2015.
11. Southern KW, Barker PM, Solis-Moya A, Patel L. Macrolide antibiotics for cystic fibrosis. Cochrane Database Syst Rev 2012;11:CD002203.
12. Kingah P, Muma G, Soubani A. Azithromycin improves lung function in patients with post-lung transplant bronchiolitis obliterans syndrome: a meta-analysis. Clin Transplant 2014;28:906-10.
13. Lam DC, Lam B, Wong MK, Lu C, Au WY, Tse EW, et al. Effects of azithromycin in bronchiolitis obliterans syndrome after hematopoietic SCT – a randomized double-blinded placebo-controlled study. Bone Marrow Transplant 2011;46:1551-6.
14. Serisier DJ. Risks of population antimicrobial resistance associated with chronic macrolide use for inflammatory airway diseases. Lancet Respir Med 2013;1:262-74.
15. Wong C, Jayaram L, Karalus N, Eaton T, Tong C, Hockey H, et al. Azithromycin for prevention of exacerbations in non-cystic fibrosis bronchiectasis (EMBRACE): a randomised, double-blind, placebo-controlled trial. Lancet 2012;380:660-7.
16. Altenburg J, de Graaff CS, Stienstra Y, Sloos JH, van Haren EH, Koppers RJ, et al. Effect of azithromycin maintenance treatment on infectious exacerbations among patients with non-cystic fibrosis bronchiectasis: the BAT randomized controlled trial. JAMA 2013;309:1251-9.
17. Valery PC, Morris PS, Byrnes CA, Grimwood K, Torzillo PJ, Bauert PA, et al. Long-term azithromycin for Indigenous children with non-cystic-fibrosis bronchiectasis or chronic suppurative lung disease (Bronchiectasis Intervention Study): a multicentre, double-blind, randomised controlled trial. Lancet Respir Med 2013;1:610-20.
18. Wong EH, Porter JD, Edwards MR, Johnston SL. The role of macrolides in asthma: current evidence and future directions. Lancet Respir Med 2014;2:657-70.
19. Albert RK, Connett J, Bailey WC, Casaburi R, Cooper JA Jr, Criner GJ, et al. Azithromycin for prevention of exacerbations of COPD. N Engl J Med 2011;365:689-98.
20. Li H, Liu DH, Chen LL, Zhao Q, Yu YZ, Ding JJ, et al. Meta-analysis of the adverse effects of long-term azithromycin use in patients with chronic lung diseases. Antimicrob Agents Chemother 2014;58:511-7.
21. Mick P, Westerberg BD. Sensorineural hearing loss as a probable serious adverse drug reaction associated with low-dose oral azithromycin. J Otolaryngol 2007;36:257-63.
22. Ray WA, Murray KT, Hall K, Arbogast PG, Stein CM. Azithromycin and the risk of cardiovascular death. N Engl J Med 2012;366:1881-90.
23. Isbister GK. Risk assessment of drug-induced QT prolongation. Aust Prescr 2015;38:20-4.
24. McCall KL, Anderson HG Jr, Jones AD. Determination of the lack of a drug interaction between azithromycin and warfarin. Pharmacotherapy 2004;24:188-94.
25. Beckey NP, Parra D, Colon A. Retrospective evaluation of a potential interaction between azithromycin and warfarin in patients stabilized on warfarin. Pharmacotherapy 2000;20:1055-9.
26. Mergenhagen KA, Olbrych PM, Mattappallil A, Krajewski MP, Ott MC. Effect of azithromycin on anticoagulation-related outcomes in geriatric patients receiving warfarin. Clin Ther 2013;35:425-30.
27. Baxter KE, Preston CL. Stockley's drug interactions: a source book of interactions, their mechanisms, clinical importance and management. 10th ed. London: Pharmaceutical Press; 2013.
28. Ten Eick AP, Sallee D, Preminger T, Weiss A, Reed MD. Possible drug interaction between digoxin and azithromycin in a young child. Clin Drug Investig 2000;20:61-4.
29. Strandell J, Bate A, Hägg S, Edwards IR. Rhabdomyolysis a result of azithromycin and statins: an unrecognized interaction. Br J Clin Pharmacol 2009;68:427-34.