

IN BRIEF

- Azithromycin has replaced clindamycin oral suspension for prophylaxis against IE in children.
- Patient compliance with azithromycin should be good as it only needs to be taken once a day for 3 days.
- Animal models support the efficacy of azithromycin as a prophylactic agent.
- Azithromycin produces high dento-alveolar tissue concentrations which persist for 7–10 days.

Azithromycin and dentistry – a useful agent?

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Objectives Azithromycin has recently replaced clindamycin oral suspension for prophylaxis of infective endocarditis (IE) in children. It is also currently recommended by the American Heart Association as an alternative to penicillin, along with clindamycin for prophylaxis of infective endocarditis in adults. The objectives of this paper were to firstly, review the current literature on the efficacy of azithromycin as a suitable prophylactic agent in the prevention of infective endocarditis; and secondly, to review its pharmacological properties as a suitable therapeutic agent in the management of odontogenic infections.

Design A review of the literature.

Conclusions The available evidence from animal models on infective endocarditis supports the efficacy of this drug as a prophylactic agent against oral streptococci. The pharmacological properties of this agent would make it a very promising therapeutic adjunct in the management of odontogenic infections. At present there are only a small number of studies available with valuable data on the efficacy of this relatively new drug. Further investigations comparing this compound with other commonly used adjuncts would be of great benefit.

INTRODUCTION

Since clindamycin syrup became unavailable, the British Society of Antimicrobial Chemotherapy (BSAC) Endocarditis Working Party has recommended azithromycin at the following doses: children under 5 years old 200 mg given 1–2 hr, children between 5–10 years old 300 mg 1–2 hr, before the procedure. Those children over 10 years old should receive the adult dose of 500 mg 1 hr before the procedure.¹ Although the incidence of IE in the paediatric population is considered to be low, over the last 20 years there has been a rising trend in the number of paediatric cases.² Several reasons may explain this phenomenon including the availability of improved diagnostic techniques for cardiac prob-

lems, use of continuous central venous catheters and cardiac implants, increasing the risk of infection, and the survival of a greater number of infants with congenital heart disease as a result of improved medical and surgical management.

In the most recent guidelines on IE prophylaxis, the American Heart Association (AHA) has also recommended azithromycin, as a single 500 mg dose 1 hr pre-operatively, as an alternative to clindamycin in adult patients.³ The aims of this paper were to review the pharmacological properties of azithromycin and the evidence for its suitability as a prophylactic agent. This paper will also review the available evidence on its suitability as a therapeutic agent for the management of odontogenic infections.

CHEMICAL AND PHARMACOLOGICAL PROPERTIES

Azithromycin is a synthetic derivative of erythromycin. Erythromycin is limited in its usefulness by its instability under the acidic conditions of the stomach, poor absorption, low blood concentrations and a reportedly limited spectrum of activity.^{4,5} The short half-life of erythromycin means that a three to four-times daily dosage schedule is required for effective treatment.⁶ In comparison, the azalide structure of azithromycin confers a much improved pharmacokinetic profile.⁷ One of the chemical features of azithromycin that distinguishes it from erythromycin is its increased stability (300 fold) at acid pH.⁸ Erythromycin is probably the single most poorly tolerated oral antibiotic. Oral administration, especially of large doses, commonly causes epigastric distress, nausea and vomiting, which may be severe. These gastrointestinal disturbances limit the maximal oral dose to 1.5 g. These side effects, however, still regularly occur with the 1.5 g dose and allergic effects occur in about 0.5% of patients. These frequent side effects are a barrier to compliance and adequate dosing. Azithromycin causes fewer gastro-intestinal side effects, and therefore compliance is greater.^{9–11} Following oral administration of azithromycin, high tissue concentrations are found, which are sustained long after serum concentrations have declined to very low levels. Azithromycin extensively penetrates cells, including tissue fibroblasts.^{12,13} It is also rapidly and extensively taken up *in-vitro* by phagocytic cells (polymorphonuclear leukocytes and macrophages). This produces intracellular concentrations far greater than those in the extracellular medium.^{13,14} Thus, azithromycin is delivered to a site of infection by two mechanisms. Firstly, by direct uptake into tissues, which in part is by fibroblasts.

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Secondly phagocytes deliver the drug to sites of infection where it is released in response to phagocytosis to deliver effective, locally high concentrations of the drug by a biological targeted delivery mechanism.^{15,16} The preferential uptake by phagocytes leads to concentrations in infected tissues, which are much higher than in similar noninfected sites.¹² Another important property of azithromycin is that in tablet, suspension and sachet form it may be given without regard to meals, further enhancing the convenience of once-daily, short-duration dosing regimens.¹⁷ The beneficial pharmacological properties are summarised in Table 1.

Table 1 Pharmacological properties of azithromycin that makes it a desirable agent in the management of dental infections

- Stable in acid pH
- Well absorbed
- Absorption not effected by food
- Sustained high tissue concentrations
- Extensive penetration of cells
- Rapid uptake by phagocytes
- Delivery in high concentrations to site of infection
- Once daily delivery
- Short duration of treatment
- Less gastro-intestinal side effects than erythromycin

The unusual pharmacokinetics of azithromycin characterised by rapid tissue penetration with simultaneous low serum levels makes it a good candidate for IE prophylaxis. The animal model of IE has been used by a number of researchers to investigate the efficacy of azithromycin for prophylaxis against oral streptococci.^{18–20}

PROPHYLACTIC USE

An investigation compared azithromycin prophylaxis with untreated controls for endocarditis in the rat model.¹⁹ A single dose of azithromycin given 24 hours before bacterial challenge was effective in preventing establishment of viridans streptococci and *Streptococcus gordonii* populations in rat heart tissue. At 24 hours after dosing the dose remaining in the serum was equal to the minimum inhibitory concentration (MIC) of the inoculated bacteria (19 mg l⁻¹). Whilst the cardiac tissue concentration was considerably higher (4.7 mg kg⁻¹). Compared with untreated infected controls six days after challenge, significantly fewer viridans streptococci or *Streptococcus gordonii* colony forming units (cfu) were recovered from the heart tissue of rats receiving a prophylactic dose of azithromycin.

The suitability of azithromycin as an effective prophylactic agent was also tested in the rabbit model of infective endocarditis.¹⁸ In this study azithromycin was compared with ampicillin in female rabbits challenged with *Streptococcus oralis*. Azithromycin and ampicillin protected 94% and 72% of animals challenged with *Streptococcus oralis*. Azithromycin was also compared with vancomycin in rabbits challenged with methicillin-resistant *Staphylococcus aureus* (MRSA). Azithromycin and vancomycin protected 59% and 94% of the methicillin-resistant *Staphylococcus aureus* (MRSA)-challenged animals, respectively. Its ability to prevent IE caused by staphylococci in this study is questionable. Prophylactic use of azithromycin in groups of patients at high risk of developing staphylococcal endocarditis cannot, therefore be recommended. This includes patients with diabetes mellitus, chronic renal failure, or chronic skin conditions and IV drug abusers, as they are often colonised with *S. aureus* (mostly MRSA strains) which are rarely susceptible to macrolides. This is an important finding, since *Staphylococcus aureus* is the second most isolated organism from cases of bacterial endocarditis, after oral streptococci.²¹

One other study investigated the efficacy of azithromycin and clarithromycin compared with that of amoxicillin, clindamycin, or erythromycin for the prevention of viridans group streptococcus (*Streptococcus milleri*) experimental endocarditis in the rabbit

model.²⁰ Infective endocarditis occurred in 88% of untreated animals, 1% of animals receiving amoxicillin, 9% of animals receiving erythromycin, 0% of animals receiving clindamycin, 2.5% of animals receiving clarithromycin, and 1% of animals receiving azithromycin. All five regimens were more effective than no prophylaxis ($P < 0.001$). Erythromycin was less effective ($P < 0.05$) than amoxicillin or clindamycin. Azithromycin or clarithromycin was as effective as amoxicillin, clindamycin, or erythromycin for the prevention of viridans group streptococcus experimental endocarditis in this model.

All of these studies support the efficacy of azithromycin as a suitable prophylactic agent for the prevention of streptococcal endocarditis. It is however, unlikely that the efficacy of antibiotic prophylaxis to prevent IE will be subjected to a randomised, placebo-controlled study in humans. Such a study would require at least 6,000 at-risk patients and would probably encounter strong ethical concerns.²²

THERAPEUTIC USES

The therapeutic benefits of azithromycin in the management of odontogenic infections has also been investigated by a number of workers.^{23–29} Azithromycin shows good bacteriostatic *in-vitro* activity against a wide variety of micro-organisms found in the mouth,³⁰ with a broad spectrum of activity towards anaerobic bacteria as well as Gram-negative bacilli.³¹ One of the problems associated with using systemic antimicrobials for the adjunctive management of odontogenic infections is patient compliance. Azithromycin has a distinct advantage because normally it only needs to be taken once daily for three days and is well tolerated in both adults and children.^{32,33} This is because it has a long half-life and good tissue penetration. Following a dose of 500 mg once daily for three days, significant tissue levels will persist in most tissues for a week to 10 days.⁷

In a study on the tissue penetration of azithromycin in patients undergoing surgery for third-molar removal, drug concentrations in plasma, saliva, gingiva and alveolar bone were evaluated.²⁶ Azithromycin concentrations detected in periodontal tissues and saliva were significantly higher than those found in plasma. The concentrations found in both saliva and the periodontal tissues were also greater than the MIC of most susceptible pathogens commonly involved in odontogenic infections. Consistent concentrations were noted for up to 6.5 days indicating the retention of this antimicrobial agent in target tissues.

Azithromycin was also compared with spiramycin in the treatment of a range of odontogenic infections.²³ In this study it proved to be superior to spiramycin, in patients with more severe disease. Furthermore, the frequency of microbial resistance was lower with azithromycin (18%) compared with spiramycin (26%). In the management of sinusitis, azithromycin has been compared with co-amoxiclav for its efficacy, tolerability and safety.²⁴ Azithromycin was found to be as effective as co-amoxiclav, with the overall clinical response rate being 87.5% and 83.7% respectively. Both drugs were equally tolerated with the same number of adverse side effects being seen between the two.

The unusual pharmacokinetic properties of this drug have also been investigated in the management of periodontal diseases.²⁵ In the treatment of chronic adult periodontitis, the adjunctive use of azithromycin was compared with a placebo to test its microbiological efficacy.²⁵ Pigmented anaerobes were found to be significantly reduced in numbers at 3 and 6 weeks compared with the placebo group and remained lower for the duration of the study (22 weeks), although not significantly. Counts of spirochaetes were significantly reduced throughout the study in patients who received azithromycin compared with placebo. In patients who had taken azithromycin there was a significant increase in the number of azithromycin-resistant oral streptococci.

ci which persisted for at least 20 weeks. This may have an effect on the suitability of using this agent prophylactically in patients who had recently received a course of azithromycin. Similarly, cross-resistance between the macrolides and clindamycin has previously been demonstrated.³⁵⁻³⁸ It is, therefore, possible for azithromycin-resistant organisms to be resistant to clindamycin. Again, it may not be advisable to use clindamycin prophylactically for the cover of IE in patients who have recently taken azithromycin or therapeutically for the treatment of periodontal disease.

In the only periodontal study to report the clinical effects of adjunctive azithromycin it was shown to be most beneficial in deeper pockets.³⁴ Longer term studies will be required to see if the beneficial effects can be demonstrated beyond the 20 weeks of this study. Although this antimicrobial agent would appear to be a useful adjunctive agent in the management of odontogenic infections there is a cost issue. A single course of azithromycin is approximately 10 times more expensive than a single course of amoxicillin or clindamycin.³⁹

CONCLUSION

It would appear that azithromycin could be a potentially useful antimicrobial agent in the management of odontogenic infections and for the prophylaxis of IE. At present there are only a small number of studies available with data on the efficacy of this relatively new drug. Further investigations comparing this compound with other commonly used adjuncts for the management of odontogenic infections would be of great benefit. The simple and short course of treatment that can be used for azithromycin may help to reduce poor patient compliance.

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