IN BRIEF

- Absorption of clindamycin produces high bone concentrations.
- Clindamycin has a favourable spectrum of activity against anaerobic infections.
- Clindamycin is not the only antibiotic to be associated with acute pseudomembranous colitis.
- The suitability of clindamycin as an effective agent for the prophylaxis of infective endocarditis has been demonstrated in the animal model.
- The use of clindamycin in the management of endodontic infections may lead to the selection of enterococci within the root canal.

Clindamycin and dentistry

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Clindamycin is an antimicrobial agent that dentists use in the UK for infective endocarditis prophylaxis but rarely for other clinical situations that require antimicrobial intervention. This has been largely due to its association with acute pseudomembranous colitis. Up to date information on the efficacy and safety of this antimicrobial agent should be known before prescription.

INTRODUCTION

The predominant use of clindamycin in dentistry in the UK has been for the prophylaxis of infective endocarditis in patients allergic to penicillin. Although it is not licensed for use in endocarditis prophylaxis, it is currently recommended by the British Society of Antimicrobial Chemotherapy (BSAC) Endocarditis Working Party as an alternative to penicillin.¹ In paediatric cases that require prophylactic cover, however, clindamycin suspension (no longer available) has been superseded by azithromycin suspension.²

The Dental Practitioner's Formulary (DPF) recommends that clindamycin should not be used routinely for the treatment of dental infections.¹ The main reason for this is because of its association

with acute pseudomembranous colitis (APC).^{3,4} Surveys have indicated that clindamycin is not frequently prescribed in the UK for the management of dentoalveolar infections.^{5,6} In other countries such as Canada there has been a resurgence in the prescribing popularity of clindamycin.⁷ The reasons for this may be related to publications in the dental literature recommending clindamycin as a first line drug in the management of odontogenic infections.^{8,9}

The purpose of this article is to review the literature on the prophylactic and therapeutic uses of clindamycin in dentistry and to discuss the association of its use with APC.

Antimicrobial activity

Clindamycin is known to have a very favourable spectrum of activity against anaerobic infections.^{10,11} Its antimicrobial spectrum also includes Gram-positive cocci, Gram-positive and -negative anaerobes and certain protozoa.¹² Although classed as bacteriostatic, bactericidal activity is usually achieved with the recommended doses¹³. The mechanism of action of clindamycin is by the inhibition of protein synthesis, acting specifically on

the 50S subunit of the bacterial ribosome. Protein synthesis is inhibited primarily in early chain elongation by interference with the transpeptidation reaction.¹³

The treatment of bacterial infections with adjunctive antimicrobials requires adequate concentrations of the antimicrobial to be obtained at the site of infection. Serum concentrations are not always equal to the concentration in the tissue. The systemic administration of clindamycin has been shown to produce high concentrations within bone.¹⁴ In mandibular bone the concentration was found to be about a third of the alveolar serum concentration, but this level exceeded the minimum inhibitory concentration of most microorganisms isolated from mandibular osteitis.¹⁵

An important feature of odontogenic infections is that they are typically polymicrobial in nature, with mixed facultative and anaerobic bacteria present. Strict anaerobes are usually the predominant bacteria, generally outnumbering the facultative anaerobes by a factor of three to four fold.¹⁶⁻¹⁸ It is therefore understandable that clindamycin has been considered a suitable antimicrobial for the management of odontogenic infections.

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Acute Pseudomembranous Colitis

Caution regarding the use of clindamycin has always been expressed due to its potential side effects. The main concern has been its association with APC, which if left untreated can be fatal. This condition appears to be related to the proliferation of antibiotic resistant *Clostridium difficile* which produces metabolites toxic to the gut wall resulting in colitis. Other micro-organisms have, however, been isolated from cases of APC, but they are rare. They include *Staphylococcus aureus*, *Clostridium perfringens* type C and *Salmonellae*.¹⁹ APC is not exclusively a side effect of clindamycin. Other commonly used antimicrobials in dentistry such as amoxicillin, erythromycin, tetracyclines, metronidazole and the cephalosporins have all been shown to cause this disease.¹⁹ In fact Bignardi reported that clindamycin was not the primary antimicrobial that is associated with colitis but was in the middle of the spectrum. Co-amoxiclav, an antimicrobial used far more frequently for the management of dental-alveolar infections, was found to be a greater risk for APC than clindamycin.²⁰

The incidence of APC following the administration of clindamycin has been stated to range from as low as 0.01% to as high as 10%.²¹⁻²³ This may reflect the populations studied as the main factors that predispose a person to APC include advanced age, debilitating illness and administration of multiple antimicrobials.²⁰ Females have been suggested to be more at risk of APC, but epidemiological studies have not supported this contention.²⁴ The incidence of reported cases of APC in the dental literature is low; in fact many authors who have done studies on the use of clindamycin have failed to note this complication.^{9,25,26} Only five dentally related cases of APC have been reported; three of the patients were elderly with an average age of 68.7 years.^{3,4,7,27,28} Previously it had been thought that prophylactic use of clindamycin would not lead to the development of APC,²⁹ but a recent case report has contradicted this contention.⁷ It is difficult to know however, if this case was caused solely by clindamycin, because the week previously the patient had received a prophylactic dose of erythromycin prior to dental treatment; the patient was aged 71.

Reports of other serious problems associated with clindamycin such as anaphylaxis are low.^{30,31} Clindamycin, however, has been shown to have neuromuscular blocking properties that may enhance the action of other neuromuscular blocking agents.^{32,33} Antagonism between erythromycin and clindamycin has been demonstrated *in vitro*, therefore these drugs should not be administered concurrently.³⁴ It has also been advised that caution

should be aired when prescribing clindamycin in patients with a history of gastrointestinal disease, especially colitis.³⁴

Prophylactic use

The prophylactic use of antibiotics is recommended by the BSAC for patients at risk of IE. Dentists are legally obliged to adhere to the guidelines laid down by the BSAC, which are published in each British National Formulary.¹ It is unlikely that a bacteraemia following a dental procedure can be totally prevented by prior prophylaxis with oral or systemic antimicrobials. It has been shown however, that the intensity of a dentally-induced bacteraemia can be reduced by prophylactic doses of antimicrobials.^{35,36}

During the decades before the 1990s, a high oral loading dose of erythromycin was recommended for penicillin-allergic patients for the prevention of IE. This recommendation was changed to clindamycin due to an accumulation of evidence on the unsuitability of erythromycin, together with the known problems of its side effects.^{37,38} Predominantly the fact is that erythromycin is the single most poorly tolerated oral antibiotic, with epigastric distress, nausea and vomiting being common. In a study on the efficacy of erythromycin stearate in the prevention of bacteraemia following dental extraction, no reduction was seen when compared with a placebo group.³⁷ Concomitant with this latter finding came evidence of failure of erythromycin to prevent IE, with the micro-organism isolated proving to be erythromycin-resistant.³⁸ Animal models of IE also reported erythromycin's failure as a suitable prophylactic agent.³⁹ Despite the change in recommendation, a recent study of prophylactic antibiotic prescribing within the National Health Service found that 18.6% of general dental practitioners would use erythromycin as a prophylactic agent in patients allergic to penicillin.⁴⁰

The suitability of clindamycin as an appropriate agent for the prophylaxis of IE has been demonstrated in the animal model.^{41,42} The protection afforded by clindamycin in these studies suggested a wide, yet theoretical, margin of safety for the use of this antimicrobial for human endocarditis prophylaxis. The American Heart Association guidelines for antibiotic prophylaxis now gives two other alternatives to clindamycin in penicillin allergic patients: azithromycin or clarithromycin are now recommended as alternatives, both as single 500mg doses.⁴³

THERAPEUTIC USES

Periodontology

Conventional periodontology treatment modalities such as scaling and root plan-

ing, periodontal surgery and maintenance are effective in the management of most periodontal diseases. In some, the systemic use of antibiotics can be a powerful adjunct to mechanical debridement. The suitability of clindamycin in the management of periodontal diseases has only been investigated in a limited number of studies.^{28,44-48} These studies have all demonstrated the beneficial effects of clindamycin as an adjunct to scaling. These results, with the exception of one study⁴⁴ may in part be related to the use of clindamycin only in patients whose subgingival micro flora was known to be susceptible to clindamycin.

The efficacy of clindamycin as an adjunctive agent in the treatment of rapidly progressive periodontitis (RPP) was compared with that of metronidazole and tetracycline.⁴⁴ The metronidazole and clindamycin groups showed a significant reduction in sulcus bleeding scores, probing depths and a significant gain in clinical attachment. Less favourable results were found in the doxycycline and placebo groups. It was concluded by the authors of this study that both metronidazole and clindamycin are effective antimicrobials when used adjunctively. All these studies indicate that clindamycin could be used as a useful periodontal adjunctive agent. Although the latest European Federation of Periodontology review, which used evidence based reviews and meta-analysis on several subject areas concluded that conclusive evidence for adjunctive benefits was only available for metronidazole and amoxicillin in combination and for spiramycin.⁴⁹

Endodontics

The treatment of acute and chronic infections of endodontic origin primarily requires operative intervention and therefore the adjunctive use of antimicrobials are not usually indicated in the healthy patient. When intervention is not possible then systemic antimicrobials are indicated to limit local spread and bring about symptomatic relief, but ultimately definitive treatment will be required.⁵⁰

Due to the predominance of anaerobic species in acute periapical infections, it was thought that clindamycin would be an appropriate adjunctive agent in the management of these infections.¹⁶ In fact interest in the micro-flora of root canals has largely been focused on anaerobic bacteria due to their predominance in untreated canals.^{17,51,52} Enterococci, which are seldom found in these circumstances, have been isolated from teeth undergoing endodontic treatment and previously root treated teeth.⁵³⁻⁵⁶ In a study of root filled teeth with apical periodontitis 69% of the bacterial strains recovered

from the root canals were facultative anaerobes.^{53,54} Enterococci were isolated in 50% of the infective cases and were the most frequently isolated. A later study on the susceptibility of enterococci isolated from root canals to various antibiotics found that 25 out of 29 strains were resistant to clindamycin.⁵⁷ These results are similar to an earlier study in which enterococci isolated were found to be completely or partially resistant to clindamycin.⁵⁸ Clindamycin has also been investigated as a topical intra-canal medicament.^{59,60} When applied as an intra-canal paste (clindamycin dissolved in saline), it was found to confer no advantage over conventional root canal dressings.⁶⁰ Another study used ethylene vinyl acetate (EVA) fibres impregnated with clindamycin. Although they were effective in significantly reducing growth of *Prevotella intermedia*, *Fusobacterium nucleatum* and *Streptococcus intermedia* in extracted teeth, enterococci were not tested.⁵⁹

The use of clindamycin in the management of endodontic infections may lead to the selection of enterococci within the canal. Empirical prescribing of systemic clindamycin may therefore not be appropriate. Culture and susceptibility testing, however, is not routinely recommended for endodontic procedures due to the risk of sample contamination.⁵⁰

Control of post-operative infection

Clindamycin has been compared with penicillin and other antibiotics for the prophylaxis of post-operative complications following third molar surgery. Clindamycin was compared with azidocillin, erythromycin and doxycycline in a double blind randomised control trial.⁶¹ This study showed that systemically administered antimicrobials offered only slight advantages in routine operations of impacted third mandibular molars. With the exception of doxycycline, these antimicrobials showed little reduction in postoperative swelling. In a similar investigation that compared penicillin with clindamycin, penicillin was seen to be marginally superior in the early post-operative period.⁶² In a more recent study, however, clindamycin treatment was found to significantly reduce the number of infections following third molar surgery as compared with amoxicillin. A combination of amoxicillin and metronidazole did produce an efficacy comparable to that of clindamycin.⁶³ The infection rate, however, following routine exodontia and dentoalveolar surgery including endodontic surgery is very low. Most dentoalveolar surgical procedures should, therefore, not require antimicrobial prophylaxis in the healthy individual to prevent infection.⁶⁴

Management of dentoalveolar abscesses

Acute dentoalveolar infections are best dealt with by establishing surgical drainage. This is not always possible or the patient may present with signs and symptoms of systemic effect. These circumstances require the use of systemic antimicrobials. Penicillin or amoxicillin, and erythromycin for penicillin allergic patients, have been regarded as antimicrobials of choice.⁶⁵

Some studies have suggested that the antimicrobial activity of penicillins have decreased against the causative bacteria related to orofacial odontogenic infections, such as streptococci and oral anaerobes. This has led to the continuing debate over whether penicillins remain adequate as the antimicrobials of choice for odontogenic infections.^{8,66-69} Clindamycin has been proposed as an alternative regime for patients with penicillin allergies or for patients for whom penicillin therapy has failed.^{8,16,69}

Concerns have also been raised about the suitability of erythromycin in the management of severe odontogenic infections.¹⁶ Erythromycin is not effective against *Fusobacterium* species and oral streptococci, which are more frequently isolated from severe odontogenic infections than milder infections.^{16,70-72}

A number of clinical trials have demonstrated clindamycin's efficacy in treating odontogenic infections. Three studies reported comparable findings when clindamycin was compared with penicillin for the management of orofacial infections.^{25,27,73} All three concluded that clindamycin would be a suitable alternative to penicillin. In a recent study into the bacteriological features and antimicrobial susceptibilities of bacteria isolated from orofacial odontogenic infections penicillin was found to be effective against most major pathogens involved.¹⁶ Although clindamycin was also found to be a suitable agent, it was suggested that clindamycin be reserved for those cases in which penicillin therapy had failed.

CONCLUSIONS

Clindamycin has good antimicrobial properties for the management of most dentoalveolar infections. These include a favourable spectrum of activity against anaerobic infections and the ability to concentrate highly in bone. Animal models support the suitability of clindamycin as a prophylactic agent and therefore it should be used in accordance with the guidelines produced by the BSAC.

The risk of developing APC with clindamycin appears low and to be no greater than many of the other antimicrobial

agents frequently prescribed in general dental practice. In the elderly or those with debilitating illnesses, however, clindamycin should not be considered a first line drug in the management of odontogenic infections.

There are few data to support the empirical prescription of clindamycin for the adjunctive management of periodontal diseases at present. Further randomised controlled studies will be required to compare its adjunctive efficacy with other antimicrobials. The potential for the selection of enterococci, following the adjunctive use of systemic clindamycin in the management of endodontic infections should be taken seriously. Enterococci are more frequently found in previously treated endodontic cases. The empirical prescription of systemic clindamycin for the management of such cases cannot be recommended.

In the management of the dentoalveolar abscess clindamycin shows comparable efficacy with penicillin. It should therefore be considered as an alternative to penicillin in penicillin allergic patients or for those cases that do not respond to penicillin.

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