Clindamycin

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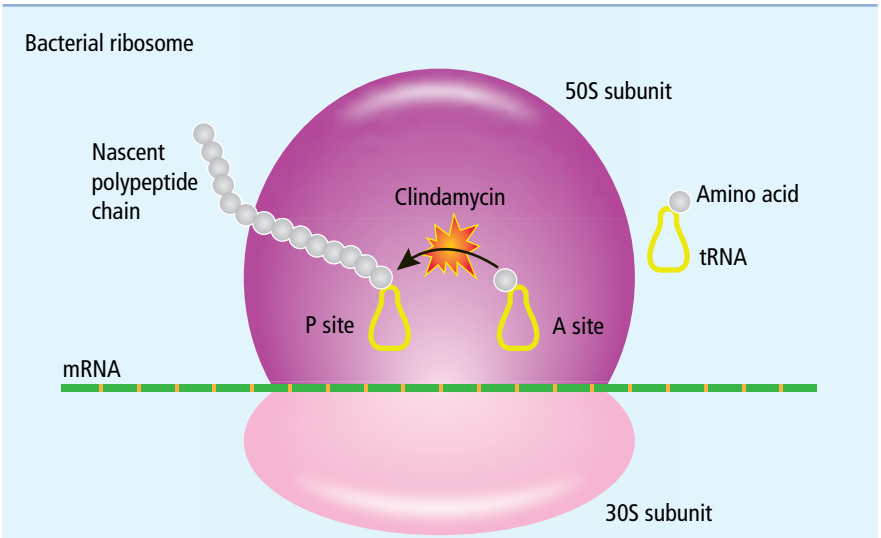

NOTES. In protein synthesis in bacteria the P (peptidyl) site of the 50S ribosomal subunit contains the nascent polypeptide chain. Transcription RNA (tRNA) charged with the next amino acid to be added to the nascent polypeptide chain binds to the acceptor (A) site on messenger RNA (mRNA). Clindamycin binds to the 50S subunit of the bacterial ribosome and suppresses protein synthesis by inhibiting transpeptidation.

Figure 1. Pharmacological action of clindamycin

Introduction

Patients with diabetes are at increased risk of soft tissue infections, particularly affecting the lower limbs. A combination of poor glycaemic control, peripheral neuropathy and peripheral vascular disease leads to large, non-healing ulcers often complicated by infection with multiple organisms, leading to significant morbidity and mortality. They also have a significant economic impact with many requiring protracted treatment as an inpatient. With increasing antimicrobial resistance the choice of antibiotic needs to be made judiciously based on the likely organism causing the infection, culture results if possible and patient specific factors. The majority of infections are caused by skin flora, in particular *Staphylococcus aureus* and other Gram-positive organisms, although Gram-negative bacilli are common in those with recurrent infections and following recent antibiotic therapy. Patients with evidence of ischaemia will likely also have anaerobic bacteria affecting their wounds and it is important to consider that there are often multiple organisms involved.

Clindamycin belongs to a small group of antibiotics known as lincosamides. It provides broad spectrum antimicrobial cover of many organisms and is licensed for use in serious intra-abdominal and skin and soft tissue infection.

Pharmacology

Clindamycin is a semi-synthetic derivative of the chemical lincomycin. By substituting a hydroxyl group with a chlorine atom it has greater bioavailability and clinical use than its predecessors. Figure 1 outlines the pharmacological action of clindamycin. It binds to the 50S ribosomal subunit and disrupts protein synthesis via interference of transpeptidation. This interference with protein synthesis inhibits cell growth and reproduction. It is bacteriostatic, and, although in some organisms it has been shown to be bactericidal at higher concentrations *in vitro*, these concentrations are too high for clinical use. Protein synthesis has an important role in toxin

mediated sepsis with infections such as Group A Streptococcus, and clindamycin therefore may also have a role in reducing the toxin burden.

Clindamycin is rapidly absorbed following oral administration, with up to 90% oral bioavailability. Serum concentrations increase in a linear fashion with increasing doses and there is no accumulative effect with prolonged prescription, allowing oral administration for mild infections and early IV to oral switch in those who are clinically stable. It has a half-life of 2–3 hours, and is mostly metabolised by the liver into active metabolites, which can then be excreted in faeces, bile or in urine. There is some evidence of enterohepatic recirculation as patients have developed *Clostridium difficile* infection (CDI) many weeks after stopping treatment.

Dose reduction or increased dosing intervals should be considered in severe hepatic impairment. Reduced renal function affects the half-life of clindamycin and increases it slightly but dose reduction is not always necessary in mild to moderate renal failure. It is not removed by dialysis.

Clindamycin has been shown to be well distributed throughout all body tissues including good bone penetration (20–75% in adults), an important factor when considering the management of complicated diabetic foot ulcers. Levels of 50% have been measured in synovial and peritoneal fluid.

Clindamycin has excellent Gram-positive and anaerobic cover allowing it to be a good choice for skin and soft tissue infection. There are also some Gram-negative bacteria which are susceptible, but clindamycin is not considered to be a first-line choice in this setting. Gram-positive cocci such as *S. aureus*, *Streptococcus pneumoniae*, Streptococcus (Groups A, C and G) and anaerobic organisms including *Bacteroides fragilis*, Fusobacterium and *Clostridium perfinogens* are all sensitive to clindamycin.

The most common side effect of clindamycin is gastrointestinal upset with many cases of anorexia, nausea, vomiting and diarrhoea and an increased incidence of CDI with this antibiotic. This was a particular problem in the 1970s with widespread use of clindamycin, but less problematic now with more prudent use. It is recommended that administration be stopped in the occurrence of diarrhoea and samples sent for CDI.

Trials of safety and efficacy

Early use against various organisms followed from the publication of small case series looking at clinical efficacy and laboratory sensitivities. One such study in 50 patients showed a good response in 44 patients, with gastrointestinal side effects reported in only one patient.[1] Such positive results led to extensive use, including in patients with diabetes. In a prospective study looking at outpatient management of uncomplicated lower extremity infections in diabetes patients, 56 were randomised to receive either clindamycin or cephalexin orally for two weeks.[2] Cultures revealed a mean of 2.1 organisms per patient. Aerobic Gram-positive organisms were the most common isolated organisms (89%). High cure rates were seen for both clindamycin and cephalexin (78% and 72% respectively).

Clindamycin may also have an important role in the suppression of toxins and virulence factors in toxin mediated sepsis.[3] Therefore the addition of this antibiotic to a regimen may enhance the management of sepsis in the immediate phase, even if the use of clindamycin is not appropriate on a longer term for that patient.

However, with widespread use the problem with gastrointestinal side effects became more obvious, particularly CDI. In a stratified analysis of case control studies, CDI that was highly resistant to clindamycin was responsible for large outbreaks of diarrhoea in four hospitals in different US states.[4] The use of clindamycin was considered to be a specific risk factor for diarrhoea due to this strain with resistance to clindamycin further increasing the risk. Resistance can occur through the alteration of the binding site and via exchange of plasmids particularly between Staphylococci and Streptococci. Clindamycin is not advised in the presence of MLSB (macrolide, lincosamide, streptogramins B) resistance, common in Streptococci and Staphylococci. This occurs due to closely related binding sites on the ribosome for macrolides and clindamycin, causing inducible clindamycin resistance in the presence of macrolides. In a recent meta-analysis that included 13 case control studies and one cohort study, the strongest association for hospital acquired CDI was for the cephalosporins and clindamycin.[5] Clindamycin should therefore be used with care and stopped if the patient develops diarrhoea.

Key points

- Soft tissue infections of lower limbs including ulceration are common in patients with diabetes
- Infections can be caused by a number of different organisms and protracted courses of antibiotics may be necessary
- Clindamycin with good oral bioavailability may be a suitable choice of antibiotic for some patients, facilitating outpatient management
- Clindamycin is associated with the development of *Clostridium difficile*, therefore patients should be advised to stop taking it if they develop diarrhoea and samples sent to test for *Clostridium difficile* toxin

Discussion

Clindamycin is an antibiotic with activity against Gram-positive and anaerobic bacteria, which are some of the most common organisms involved in skin and soft tissue infections in patients with diabetes.

It is a useful additional therapy particularly if patients are very unwell or not clinically responding, and is a useful alternative in those with penicillin allergy. In penicillin allergic patients, where broad spectrum Gram-positive and Gram-negative cover is required, the combination of clindamycin and ciprofloxacin can be used, but with an increased risk of CDI.

Careful consideration of CDI should be given to patients should they develop diarrhoea.

Declaration of interests

There are no conflicts of interest declared.

References

References are available online at www.practicaldiabetes.com.

References

1. Geddes AM, *et al.* Clinical and bacteriological studies with clindamycin. *BMJ* 1970;2:703–4.
2. Lipsky BA, *et al.* Outpatient management of uncomplicated lower extremity infections in diabetic patients. *Arch Int Med* 1990;150:790–7.
3. Stevens DL, *et al.* Impact of antibiotics on expression of virulence-associated exotoxin genes in methicillin sensitive and methicillin resistant *Staphylococcus aureus*. *J Infect Dis* 2007; 195:202–11.
4. Johnson S, *et al.* Epidemics of diarrhea caused by a clindamycin resistant strain of *Clostridium difficile* in four hospitals. *New Engl J Med* 1999;341: 1645–51.
5. Slimings C, Riley TV. Antibiotics and hospital-acquired infection: update of systematic review and meta-analysis. *J Antimicrob Chemother* 2014;69: 881–91.