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MINI-REVIEW

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Lincomycin, clindamycin and their applications

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Abstract Lincomycin and clindamycin are lincosamide antibiotics used in clinical practice. Both antibiotics are bacteriostatic and inhibit protein synthesis in sensitive bacteria. They may even be bactericidal at the higher concentrations that can be reached in vivo. Clindamycin is usually more active than lincomycin in the treatment of bacterial infections, in particular those caused by anaerobic species; and it can also be used for the treatment of important protozoal diseases, e.g. malaria, most effectively in combination with primaquine. Resistance to lincomycin and clindamycin may be caused by methylation of 23S ribosomal RNA, modification of the antibiotics by specific enzymes or active efflux from the periplasmic space.

Introduction

Although several hundred synthetic and semisynthetic derivatives of lincosamides (Magerlein 1971) and almost 20 biosynthetic fermentation derivatives have been prepared (Piepersberg and Distler 1997; Spizek and Rezanka 2004) only two of them, viz. clindamycin and lincomycin A, are used in clinical practice (Kucers et al. 1997).

The former is prepared semisynthetically and the latter is isolated from fermentations of *Streptomyces lincolnensis*. As shown in Table 1, all other derivatives are not suitable, either due to their low biological activity or high toxicity or for other reasons. Therefore, in the present review we concentrate on the two previously mentioned and commercially produced antibiotics.

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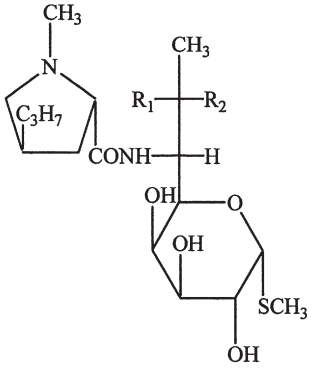
Chemical structure and mode of action

Lincomycin and clindamycin are white to light-yellow substances forming salts and esters with acids (Structure 1).



They are readily soluble in water and chemically are extraordinarily stable in both the dry state and in solution. Lincomycin is used as a hydrochloride and clindamycin is used as a phosphate ester (dihydrogenphosphate of clindamycin). In the human organism, free clindamycin is released by the action of phosphatases. The ester alone does not exhibit any antibacterial activity.

Although the chemical structure of macrolides (e.g. erythromycin), lincosamides (e.g. lincomycin, clindamycin, celesticetin) and streptogramins is very different, their mechanism of action is identical. All the antibiotics block protein synthesis in sensitive bacterial strains by inhibiting the peptidyltransferase reaction on the 50S ribosomal subunit. In accordance with their mechanism of action, bacteria quite often develop cross-resistance to macrolides, lincosamides and streptogramin B. Lincomycin and clindamycin not only share a common mechanism of action in sensitive microorganisms but also exhibit a similar antibacterial spectrum and usually also develop cross-resistance. Clindamycin inhibits bacterial protein synthesis and acts specifically on the 50S subunit of the bacterial ribosome, most likely by affecting the process of peptide

Table 1 Antibacterial activities of 7-substituted-7-deoxylincomycins. R_1 and R_2 are shown in Structure 1

Compound	Standard curve assay with *Sarcina lutea*	Serial dilution minimal inhibitory concentration					
		Staphylococcus aureus UC 76	*S. aureus* UC 3235	*S. faecalis*	*Escherichia coli*	*Proteus vulgaris*	*Salmonella schottmuelleri*
R_1=OH, R_2=H (lincomycin)	1.0	0.4	0.8	12.5	400	800	4,000
R_1=H, R_2=Cl (clindamycin)	4.0	0.1	0.1	6.2	25	250	64
R_1=H, R_2=Br	4.0	0.05	0.05	6.2	100	100	50
R_1=H, R_2=I	4.0–5.0	0.05	0.05	3.2	12.5	50	50
R_1=R_2=H	0.3	1.6	1.6	6.4	>200	>200	>200
R_1=H, R_2=N_3	0.8	0.4	0.4	25	>200	>200	>200
R_1=H, R_2=NH_2	0.01	50	50	100	>200	>200	>200
R_1=H, R_2=CN	0.8	0.8	0.4	25	>200	>200	>200
R_1=R_2=O	0.02	50	50	50	>200	>200	>200
R_1=H, R_2=OH	0.5	1.6	1.6	25	>200	>200	>200
R_1=Cl, R_2=H	2.0	0.8	0.8	12.5	>200	>200	>200
R_1=SH, R_2=H	0.1	3.2	3.2	200	>200	>200	>200
R_1=H, R_2=SH	0.3	1.6	1.6	100	>200	>200	>200

chain initiation. It may also stimulate dissociation of peptidyl-tRNA from ribosomes. *Escherichia coli*, although generally intrinsically resistant, shows a lower adherence to buccal mucosal cells when exposed to subminimal inhibitory concentrations of clindamycin, which may be due to protein synthesis inhibition.

Presumably, it was suppression of protein synthesis which enabled Sanders et al. (1983) to show that clindamycin is an effective in vitro inhibitor of the derepression of bacterial β-lactamases, which would otherwise be produced by certain non-fastidious Gram-negative bacilli exposed to various β-lactam antibiotics. Similarly, Schlievert and Kelly (1984) showed that levels of clindamycin that do not inhibit bacterial growth can inhibit toxin production in toxic shock syndrome-producing strains of *Staphylococcus aureus*.

When usual doses are applied, both lincomycin and clindamycin exhibit bacteriostatic activity. At the higher concentrations that can be reached in vivo, their effect may even be bactericidal. However, the onset of the bactericidal effect is delayed and is less complete than that of e.g. β-lactams. It increases generally in parallel with increasing concentration of antibiotic and, even in this respect, clindamycin is more effective than lincomycin. However, the main advantage of lincomycin is that it can be applied at a substantially wider range of clinically therapeutic doses.

Macrolides and lincosamides are first choice bacteriostatic antibiotics used in veterinary dermatology. The main

Table 2 Effect of lincomycin and clindamycin on some common pathogenic bacteria. These values serve for a general orientation only. They were obtained from a number of experimental papers (e.g. Magerlein 1971; Kucers 1997; Smieja 1998) in which different strains were used and the data often varied substantially

Test organism	Minimum inhibitory concentration (μg/ml)	
	Lincomycin	Clindamycin
Gram-positive	Generally sensitive	Generally sensitive
Bacillus anthracis	0.25–8.0	0.25–5.0
Staphylococcus aureus	0.2–3.2	0.04–1.6
Sta. epidermidis	0.4–1.8	0.1–0.2
Streptococcus agalactiae	0.1–0.2	0.02–0.1
Str. pneumoniae	0.01–0.8	0.002–0.1
Str. pyogenes	0.04–0.8	0.01–0.2
Str. viridans	0.02–1.0	0.005–0.2
Gram-negative	Generally resistant	Generally resistant
Escherichia coli	1,000	64
Haemophilus influenzae	4–16	0.5–16.0
Klebsiella pneumoniae	8	125
Neisseria gonorhoeae	8–64	0.5–4.0
N. meningitis	>32	4
Proteus vulgaris	1,000	250
Pseudomonas aeruginosa	>1,000	1,000
Salmonella schottmuelleri	125	64

antibiotics applied are erythromycin, lincomycin, clindamycin and tylosin. They are well absorbed if given orally and are able to penetrate well into infected skin. Their spectrum of action comprises bacteria commonly associated with skin infections, including staphylococci. Their main disadvantages are the rapid development of bacterial resistance and occasional gastrointestinal upset (Noli and Boothe 1999).

Macrolides, fluoroquinolones, rifamycins, tetracyclines, trimethoprim-sulfamethoxazole and clindamycin are described as the antimicrobial agents of preference for the dermatologist (Epstein et al. 1997). Clindamycin administration results in changes in the intestinal microflora. The numbers of enterococcal species increase and those of all anaerobes decrease.

Some antibiotics also exhibit immunomodulatory effects, clindamycin among them (VanVlem et al. 1996). Clindamycin also affects some protozoa, e.g. *Toxoplasma gondii*, *Plasmodium falciparum* and *Pneumocystis carinii*. Clindamycin (450–600 mg administered every 6 h) and 15–30 mg of primaquine base applied once a day were successfully used for the treatment of infections caused by *Pne. carinii* (Fishman 1998), whereas lincomycin did not exhibit any activity.

Remington (1990) demonstrated that a combination of clindamycin with primaquine is highly effective in the treatment of pneumonia caused by *Pne. carinii*, even in AIDS patients.

In general, common Gram-positive cocci, except for true enterococci, are sensitive to lincomycin and clindamycin. In contrast, most Gram-negative bacteria are usually intrinsically resistant to lincomycin and clindamycin (see Table 2). Most anaerobic bacteria, both Gram-positive and Gram-negative, are sensitive to lincomycin and clindamycin. However, clindamycin is usually much more efficient against some important anaerobes than lincomycin and also affects protozoa.

The lincosamides lincomycin and clindamycin belong to the antibiotics acting on translational machinery (Harms et al. 2003). They interact with both the A-site and the P-site on the 50S ribosomal subunit, hampering the positioning of both tRNA molecules and directly inhibiting peptide bond formation.

Protein synthesis is one of the most common mechanisms of action of many antibiotics and ribosomes are a major target. In order to elucidate the structural basis of ribosome–antibiotic interactions, Schlunzen et al. (2001) determined high-resolution X-ray structures of the 50S ribosomal subunit of *Deinococcus radiodurans*, complexed with several clinically important antibiotics, such as chloramphenicol, clindamycin and three macrolides, viz. erythromycin, clarithromycin and roxithromycin. The authors found that the antibiotic binding sites are composed of segments of 23S ribosomal RNA at the peptidyl transferase cavity only and that no interaction of the drugs with ribosomal proteins is involved. They thus concluded that the antibiotics investigated, including clindamycin, interact exclusively with the peptidyl transferase center in eubacteria.

The effect of lincomycin and clindamycin conformations on ribosome-binding was investigated by Verdier et al. (2000), who used two-dimensional transferred nuclear Overhauser spectroscopy, resulting in a bound structure compatible with experimental NMR data. Clindamycin, the biologically more active antibiotic, exhibited a stronger NMR response than lincomycin, indicating that a low-affinity binding level is associated with the tight binding which is related to biological activity. Superimposition of lincosamide-, macrolide- and ketolide-bound structures were found to exhibit conformational similarities, in agreement with the proposed partial overlapping of lincosamide and macrolide binding sites.

The translational functions of bacterial chromosomes are the target for a large number of antimicrobial agents. The 14- and 16-membered macrolides, the lincosamides and the streptogramin B compounds were shown to have some similar inhibitory properties. The 14-membered macrolides, such as erythromycin, have the same inhibitory effect on the translation and formation of the 50S ribosomal subunit in growing bacterial cells. Champney and Tober (2000) tested the 16-membered macrolides spiramycin and tylosin, the lincosamides lincomycin and clindamycin and three streptogramin B compounds (pristinamycin I-A, virginiamycin S, CP37277) in *Sta. aureus*. They found that each of these compounds inhibited specifically the formation of the 50S subunit, in addition to exhibiting an inhibitory effect on translation. In contrast, two streptogramin A compounds, virginiamycin M1 and CP36296, similarly to chloramphenicol, were effective inhibitors of translation without showing a specific effect on the assembly of the large ribosomal subunit. Virginiamycin M1 and pristinamycin I-A demonstrated a synergistic inhibitory effect on protein synthesis without specifically inhibiting the 50S subunit formation. It thus appears that the entire class of MLSB antibiotics inhibit the 50S subunit assembly and also have common ribosome-binding sites and inhibitory functions.

The relative antimicrobial activity of clindamycin phosphate and clindamycin was investigated and the effect of skin homogenates on the activity of clindamycin phosphate was studied. Minimum inhibitory concentration (MIC) values were determined in dermally relevant organisms; and bactericidal activity was studied using time–kill methodology. The effect of skin homogenates on the antimicrobial activity of clindamycin phosphate was studied by well-diffusion assay. The MIC of clindamycin was substantially lower than that of clindamycin phosphate in all susceptible organisms. Clindamycin also showed greater bactericidal activity (rate of kill) than clindamycin phosphate. Phosphatases in skin homogenates activated clindamycin phosphate at pH 4–8 with a maximal activation at pH 4 (Amr et al. 2001).

Sztaricskai et al. (1996) investigated the relative antimicrobial activity of clindamycin and clindamycin phosphate and the effect of skin homogenates on the activity of clindamycin phosphate. Clindamycin was found to exhibit a higher bactericidal activity than clindamycin phosphate.

Phosphatases of skin homogenates activated clindamycin phosphate with a maximum activation at pH 4.

The topical retinoid class of drugs, including tretinoin, adaptalene and tazarotene, and the topical antibacterials clindamycin and erythromycin are used for the treatment of acne. The drugs, when administered appropriately, deliver minor amounts of active ingredients into the circulation. The application of clindamycin may exceptionally lead to diarrhea and pseudomembranous colitis (Akhavan and Bershad 2003).

Treatment of acne with clindamycin/benzoyl peroxide gel was reviewed by Warner and Plosker (2002). In this combination, clindamycin inhibits bacterial protein synthesis by binding to the 50S ribosomal subunits and causing the inhibition of peptide-bond formation, whereas benzoyl peroxide decreases inflammatory damage by inhibiting the release of reactive oxygen species from polymorphonuclear leukocytes (PMNs) through the killing of these cells. Clindamycin also suppresses the complement-derived chemotaxis of polymorphonuclear leukocytes in vitro, thereby reducing the inflammation potential.

Clindamycin is commonly used for the treatment of intra-abdominal infections, recurrent group A streptococcal pharyngitis, invasive group A streptococcal infection, *Chlamydia trachomatis* cervicitis, anaerobic lung infections and bone and soft tissue infections. It is also used for the treatment of diabetic foot infections. Its high cost is one of the main disadvantages of clindamycin, together with the occurrence of rash and the predisposition of patients treated with clindamycin to *Clostridium difficile* infections (Smieja 1998).

The study by Hopkins and Macfarlane (2003) used cultural and molecular techniques to investigate the bifidogenicity of three nondigestible oligosaccharide (NDO) preparations in normal and antibiotic-treated fecal microbiotas in vitro and their ability to increase barrier resistance against colonization by *Clo. difficile*.

Resistance

In principle, the basic mechanisms of antibiotic resistance include microbial cell impermeability, target site modification, enzymatic modification or destruction of the antibiotic and its increased efflux.

The main type of resistance to lincomycin and clindamycin is the resistance that renders a sensitive microorganism resistant to macrolides, lincosamides and streptogramin B (MLS_B resistance). This type of resistance is associated with genes encoding methyltransferases modifying the common target site of macrolides and lincosamides, i.e. 23S ribosomal RNA (e.g. genes *ermA* and *ermC*). The expression of MLS_B resistance in Gram-positive cocci may be constitutive or inducible. The induction of MLS_B resistance varies by species, and in most Gram-positive species, erythromycin is a more effective inducer of resistance than clindamycin.

Staphylococci can also owe their resistance to lincosamides to the enzymatic inactivation of these drugs. Inactivation (resistance) of lincosamides in *Sta. aureus* is based on transformation by the enzyme product of the *linA* genes, viz. 3-lincomycin 4-clindamycin *O*-nucleotidyltransferase (Matsuoka 2000).

The third resistance mechanism to clindamycin involves active efflux of the antibiotic from the periplasmic space. This mainly occurs in Gram-negative bacteria. The gene *msrA* was described in staphylococci encoding the protein responsible for the active efflux of these antibiotics.

The occurrence of some genes involved in MLS_B-resistance in methicillin-resistant strains of *Sta. aureus* may vary in different countries. In the Czech Republic, the genes *ermC* and *ermA* are the most frequent determinants of MLS_B resistance, while less common is the gene *msrA*, encoding the protein responsible for the active excretion of macrolides and streptogramins but not lincosamides by the resistant cells. The gene *linA*, whose protein product modifies and thus inactivates lincosamide antibiotics only, is an additional resistance gene that is even less frequent (Novotná et al. 2002).

Lincomycin resistance in clinical isolates of staphylococci and streptococci has been recognized for several decades. This resistance is plasmid-mediated and is encoded on transposons. The plasmids that mediate lincomycin resistance in streptococci and staphylococci are highly similar structurally, indicating that they could be readily transferred among strains of these species.

The resistance of enterococci and staphylococci to many antibiotics, including clindamycin, was described by McManus (1997); and the antibiotic resistance of different strains of *Bacteroides*, *Prevotella* and *Porphyromonas* species and their in vitro antimicrobial susceptibility to many antibiotics, including clindamycin, were reviewed by Falagas and Siakavellas (2000).

Effect on Gram-positive bacteria

The effects of lincosamides on Gram-positive bacteria are summarized in Table 2. Clindamycin is active against most of the following bacteria: *Sta. aureus*, *Str. pyogenes*, *Str. pneumoniae*, *Str. viridans* and *Str. bovis*, *Corynebacterium diphtheriae*, *Enterococcus durans*, *Bacillus anthracis*, *Bac. cereus* and *Nocardia* spp but, unfortunately, it is inactive against *Ent. faecalis* and *Ent. faecium*. In stomatology, clindamycin can be used for the treatment of infections caused by *Bac. melaninogenicus* and *Bac. fragilis*. Bacterial skin and skin structure infections are caused by aerobic staphylococci and streptococci (*Str. pyogenes*, *Sta. aureus*), with aerobic Gram-negative bacilli and anaerobes being involved in more complicated infections. Systemic therapy with lincosamides (clindamycin) has been primarily used for the treatment of these infections for many years (Guay 2003).

Sta. aureus and *Str. pyogenes* cause a number of serious infections, such as necrotizing fasciitis and toxic-shock syndrome, which are associated with the release of bacterial toxins. Animal studies have demonstrated clin-

damycin to be more effective in treating these severe infections than other drugs (Coyle 2003).

Depending on the mode of infection, *Bac. anthracis* infection can occur in three forms: cutaneous, gastrointestinal and inhalation. Anthrax is a zoonotic disease but the inhalation form can also be used as a biological warfare agent. In addition to other antibiotics, clindamycin can be used for its treatment (Brook 2002a).

Severe infections due to *Str. pyogenes* (group A streptococci) can be treated with clindamycin, acting as an inhibitor of the synthesis of protein M and extracellular proteins (Bouvet 1996). The treatment of pneumonia caused by *Bac. cereus* with clindamycin was described by Bastian et al. (1997).

In spite of the fact that tests of clindamycin resistance in streptococci are not regularly performed in clinical practice, resistance to clindamycin has already been detected in strains of *Str. pyogenes*, strains of Group B streptococci and strains of *Str. pneumoniae*. Pneumococci multiresistant to many antibiotics, including clindamycin, have been reported from South Africa, but in most areas in the United States, they are still clindamycin-sensitive. Staphylococci resistant to clindamycin are more common and clindamycin sensitivity tests are always performed. However, the situation is rapidly changing and the numbers of clindamycin-resistant pneumococci and staphylococci appear to be permanently on the increase.

The increasing prevalence of clindamycin-resistant bacteria (resistant *Str. pneumoniae* in particular) is leading to new approaches to the management of common respiratory infections in the outpatient setting (Green and Wald 1996).

Clindamycin is an effective therapy for community-acquired, methicillin-resistant *Sta. aureus*, but there is a risk of the development of clindamycin resistance during the treatment of these bacteria (Marcinak and Frank 2003). Staphylococci resistant to clindamycin are more common and clindamycin sensitivity tests are always performed (Reeves et al. 1991). Methicillin-resistant strains of *Sta. aureus* that are also resistant to clindamycin are becoming frequent in the Czech Republic (Melter 2003).

Emerging treatments for streptococcal toxic-shock syndrome (caused by e.g. *Str. pyogenes*) include the administration of clindamycin and intravenous gammaglobulin (Stevens 2000).

Str. pyogenes products, particularly the capsule, protein M and streptococcal toxins, cause severe septic and toxic syndromes. Clindamycin should be used in the case of septic shock (Veyssier-Belot et al. 1999).

The efficacy of clindamycin and the failure of penicillin to treat a severe group A streptococcal infection and streptococcal toxic shock syndrome were described by Stevens (1996).

Siberry et al. (2003) reported infection caused by clindamycin-susceptible, erythromycin-resistant, methicillin-resistant *Sta. aureus* (MRSA) that did not respond to the treatment with clindamycin. The MRSA isolate obtained after treatment with clindamycin was resistant to clindamycin but was found to be identical by pulsed-field electrophoresis to the clindamycin-susceptible isolate obtained before treatment. The erythromycin induction test (D test) revealed in vitro inducible macrolide–lincosamide streptogramin B resistance (iMLS) in the pretreatment isolate. The testing confirmed in vitro iMLS in 56% of erythromycin-resistant, clindamycin-susceptible clinical *Sta. aureus* isolates and in a significantly higher proportion (78%) of methicillin-susceptible *Sta. aureus* isolates from pediatric patients. It thus appears that all *Sta. aureus* isolates should be tested for iMLS before clindamycin susceptibility is reported.

Susceptibilities of recent clinical isolates of *Str. pneumoniae* to 19 antibiotics were investigated. The frequency of erythromycin nonsusceptibility was high, i.e. 8/13 (61.5%), 10/14 (71.4%) and 11/11 isolates (100%) from 13 penicillin-susceptible, 14 penicillin-intermediate and 11 penicillin-resistant *Str. pneumoniae*, respectively. Macrolide resistance was detected by means of polymerase chain reaction (PCR) and disk-diffusion methods. Of these erythromycin-nonsusceptible pneumococcal isolates, 13/29 (44.8%) isolates contained genomic copies of *mefA* and showed non-D-shaped inhibitory zones observed around rokitamycin and/or clindamycin disks. Sixteen out of 29 isolates (55.2%) contained copies of *ermB* and showed typical D-shaped zones of inhibition, except one isolate. Although the macrolide resistance determinants, *mefA* and *ermB*, could be identified by PCR and disk-diffusion methods, PCR methods were more reliable in elucidating these determinants. The susceptibility pattern to 14-, 15- and 16-membered macrolides and clindamycin differed between the $mefA^+$ and $ermB^+$ isolates (Kimura et al. 2003).

An enhanced bactericidal response against β-hemolytic streptococci has been found with a combination of penicillin and clindamycin (Seal 2001). The true fungi and *Mycobacterium tuberculosis* are clindamycin-resistant, but clindamycin has some activity against *Myc. leprae*.

Effect on Gram-negative bacteria

The effect of lincomycin and clindamycin on some Gram-negative bacteria is summarized in Table 2. Practically all aerobic Gram-negative bacteria are resistant to clindamycin. It was shown that in vitro clindamycin is more active against *Hemophilus influenzae* than lincomycin. *Campylobacter jejuni* is sensitive to clindamycin, but *Cam. coli* is much more resistant (128 μg/ml), as compared with *Cam. jejuni* (8 μg/ml). *Capnocytophaga canimorosus* causing bacteremic illness and dog sickness or other animal diseases is clindamycin-sensitive. Flavobacteria may also be clindamycin-sensitive (Sheridan et al. 1993). Leng et al. (1975) used combinations of clindamycin with gentamicin against Enterobacteriaceae and *Pseudomonas aeruginosa* and demonstrated synergism. Klastersky and Husson (1977) showed that gentamicin did not interfere with the activity of clindamycin against *Bac. fragilis* and that

clindamycin did not influence the activity of gentamicin against *Esc. coli*.

Mycoplasma and *Ureaplasma urealyticum* are clindamycin-resistant, although clindamycin has some activity against *Chl. trachomatis* (Rice et al. 1995) and *Coxiella burnetii*.

Adjunctive use of clindamycin along with mechanical debridement is recommended as an acceptable therapeutic regimen for the treatment of the Gram-negative, facultatively anaerobic *Actinobacillus actinomycetemcomitans*-associated periodontitis (Walker and Karpinia 2002).

Laboratory results could be used in clinical practice by comparing the MIC_{50} of the germs regularly encountered in bone infections (staphylococci, streptococci including enterococci, Gram-negative bacilli, *Pse. aeruginosa*, *Hem. influenzae*) with the concentrations obtained in the different studies. In studies by Boselli and Allaouchiche (1999), it was described that clindamycin has a moderate bone diffusion.

Effect on anaerobic bacteria

In general, lincomycin and clindamycin inhibit anaerobic bacteria; and it is infections caused by anaerobic bacteria that are therapeutically treated with these drugs.

Clo. tetani and *Clo. perfringens* are sensitive to clindamycin; but some strains of *Clo. perfringens* and strains of *Clo. sporogenes*, *Clo. tertium*, *Clo. bifermentans*, *Clo. novyi*, *Clo. ramosum* and *Clo. sordelli* may be clindamycin-resistant.

Clo. difficile is now established as a major nosocomial pathogen. *Clo. difficile* infection is seen almost exclusively as a complication of antibiotic therapy and is particularly associated with clindamycin and third-generation cephalosporins (Freeman and Wilcox 1999). Agents with a high potential to induce *Clo. difficile*-associated disease include aminopenicillins, cephalosporins and clindamycin (Job and Jacobs 1997).

Clo. difficile is responsible for 300,000–3,000,000 cases of diarrhea and colitis in the United States every year. The antibiotics most frequently associated with this infection are clindamycin, ampicillin, amoxicillin and cephalosporins (Mylonakis et al. 2001).

Clindamycin was shown to be an effective drug in the treatment of Gram-positive anaerobic infections (e.g. *Clo. perfringens*). The first very effective bactericidal anti-anaerobic drug was metronidazole, introduced to clinical practice in the early 1980s. Sometimes penicillin G and chloramphenicol were used successfully in anaerobic infections. Very rapidly, the anti-anaerobic armamentarium was extended with clindamycin, cefoxitin, imipenem, co-amoxyclav and piperacillin-tazobactam. The resistance rate to metronidazole and imipenem remains low, but clindamycin has seen an important decrease in bacterial susceptibility (Bryskier 2001). A systematic review of studies that investigated the association of clindamycin-like antibiotics with hospital-acquired *Clo. difficile* diarrhea was undertaken to summarize the strength of the evidence for this relationship (Thomas et al. 2003).

Agents with a high potential to induce *Clo. difficile*-associated disease include aminopenicillins, cephalosporins and clindamycin (Job and Jacobs 1997).

All other anaerobic Gram-positive organisms, such as *Peptococcus*, *Peptostreptococcus*, *Propionibacterium*, *Bifidobacterium* spp, *Lactobacillus* spp, *Actinomyces israelii*, *Bifidobacterium* spp and *Eubacterium* spp (Brook and Frazier 1993), are usually sensitive to clindamycin. Naturally, even here, resistant strains have been described, e.g. *Peptostreptococcus* spp (Reig et al. 1992b) and *Lactobacillus* spp.

Vaginal bacterial infections are usually caused by mixed bacterial populations, including *Peptostreptococcus* sp., *Peptococcus* sp., *Bacteriodes fragilis* and aerobic bacteria such as *Str. viridans*, *Str. agalactiae* and, to a less extent, *Str. pyogenes* and other enterobacteria. The mixed population can also contain enterococci and staphylococci. With the exception of enterococci, the population is to a considerable extent sensitive to a combination of clindamycin with an aminoglycosidic antibiotic. Clindamycin was also found to inhibit *Chl. trachomatis* (Ridgway et al. 1978). Bacterial vaginosis is caused by an alteration in the vaginal flora, where the normally predominant lactobacilli are replaced by a cocktail of organisms including *Gardnerella vaginalis* and anaerobes and is treated with metronidazole or clindamycin (Priestley and Kinghorn 1996). In bacterial vaginosis, the normal hydrogen peroxide-producing *Lactobacillus* sp. in the vagina is replaced with high concentrations of characteristic sets of aerobic and anaerobic bacteria. It also occurs in women treated e.g. by orally administered clindamycin (McGregor and French 2000).

Clindamycin exhibits a good activity against the anaerobic group of *Bacteroides fragilis* (2 μg/ml). Unfortunately, the number of clindamycin-resistant strains is increasing with time, but *Bct. fragilis* still remains one of the most sensitive strains, as compared with *Bct. thetaiotaomicron*, *Bct. ovatus*, *Bct. vulgatus* and *Bct. distasonis* (Tanaka-Bandoh et al. 1995). For instance, in the United States the resistance is very low, varying to up to 25% of strains. Unfortunately, as usual, it increases proportionally with time. Thus, in the *Bct. fragilis* group, it has increased from 4% to 38% in 10 years. A similar situation is also observed in other parts of the world (Patey et al. 1994; Turgeon et al. 1994) and it is apparent that this resistance must still be increasing even further.

Clindamycin is quite active against other Gram-negative anaerobes, such as *Prevotella disiens* and *Pre. melaninogenica* and the *Fusobacterium* spp. *Bct. gracilis* may be clindamycin-sensitive but some strains are resistant. Some but not all strains of Gram-negative anaerobic bacilli, such as *Butyrivibrio*, *Succinimonas* and *Anaerovibrio*, were described as sensitive to clindamycin. Necrotizing fasciitis continues to occur due to β-hemolytic streptococci, but is now also recognized as being also due to *Vibrio* spp in fishermen and those in contact with warm water in the Gulf of Mexico and South-East Asia, including Hong

Kong. An enhanced bactericidal response against β-haemolytic streptococci has been found with a combination of penicillin and clindamycin (Seal 2001). The mechanism of *Bacteroides* spp resistance to clindamycin is usually as in Gram-positive bacteria (Jimenez-Diaz et al. 1992; Reig et al. 1992a). The resistance gene in *Bacteroides* spp can be located on plasmids or on the chromosome; and it can be transferred between species by a plasmid or transposon.

In cases of anaerobic sepsis, usually caused by *Bct. fragilis* or *Peptostreptococcus* sp., the application of clindamycin as the first choice antibiotic is fully justified. In many patients with acne, caused by resistant *Propionibacterium acnes*, continued treatment with antibiotics such as clindamycin can be inappropriate or ineffective (Cooper 1998).

Clo. difficile may be clindamycin-sensitive or resistant and the proportion of sensitive strains has varied from 10% to 90% in different studies. During outbreaks of diarrhea associated with *Clo. difficile*, the strains are usually clindamycin-resistant and contain a plasmid which codes for a transferable MLS_B resistance. This resistance can be transferred from *Clo. difficile* to *Sta. aureus*. In one study, almost all 161 isolates of *Clo. difficile* in serogroups A, F, G, H and X were susceptible to clindamycin and other antibiotics, but 32 toxigenic isolates of serogroup C were clindamycin-resistant. Clindamycin exhibits an antibacterial effect on other Gram-negative anaerobes, such as *Pre. disiens*, *Pre. melaninogenica* and *Fusobacterium* spp. *Bct. gracilis* may be clindamycin-sensitive but some strains are resistant. Some but not all strains of Gram-negative anaerobic bacilli, such as *Butyrivibrio*, *Succinimonas* and *Anaerovibrio*, were described as sensitive to clindamycin.

The microbiology, diagnosis and management of bacteremia caused by anaerobic bacteria (*Bct. fragilis*, *Peptostreptococcus* sp., *Clostridium* sp., *Fusobacterium* sp.) in children were reviewed by Brook (2002b).

Teng et al. (2002) studied the susceptibility of 16 different antimicrobial agents by determining MIC values in 344 isolates of anaerobic bacteria obtained from patients with significant infections. β-Lactams were more efficient in Gram-positive than in Gram-negative anaerobes. In all species, piperacillin-tazobactam was the most active among β-lactam-β-lactamase inhibitors. Resistance to clindamycin was higher (50–70%) than that to cefoxitin (31–65%) in species of the *Bct. fragilis* group other than *Bct. fragilis* itself (4% resistant to cefotoxin, 33% resistant to clindamycin). *Bct. thetaiotaomicron* was the most resistant to both clindamycin (70%) and cefotoxin (65%). The results obtained show clearly that the incidence of cefotoxin and clindamycin resistance among anaerobes is high and that resistance to clindamycin in anaerobes is always higher than that to cefotoxin.

To elucidate *Cam. jejuni* resistance to antibiotics in Germany, MICs of different antibiotics, e.g. ciprofloxacin, moxifloxacin, erythromycin, clindamycin and tetracycline, were determined for 144 clinical isolates. The data indicated a considerable ciprofloxacin resistance (45.1%) without a clonal relationship of the strains and a greater in vitro activity of moxifloxacin, erythromycin and clindamycin (Wagner et al. 2003). It is worth mentioning that the breakpoints for resistance to erythromycin and clindamycin were practically identical (8 μg/ml), in agreement with their mechanism of action and resistance.

The susceptibilities of recent clinical isolates of *Str. pneumoniae* to 19 antibiotics were investigated. The frequency of erythromycin nonsusceptibility was high, i.e. 8/13 (61.5%), 10/14 (71.4%) and 11/11 isolates (100%) from 13 penicillin-susceptible, 14 penicillin-intermediate and 11 penicillin-resistant *Str. pneumoniae*, respectively. Macrolide resistance was detected by means of PCR and disk-diffusion methods. Of these erythromycin-nonsusceptible pneumococcal isolates, 13/29 (44.8%) isolates contained genomic copies of *mefA* and showed non-D-shaped inhibitory zones around rokitamycin and/or clindamycin disks. Sixteen out of 29 isolates (55.2%) contained copies of *ermB* and showed typical D-shaped zones of inhibition, except one isolate. Although the macrolide resistance determinants, *rnefA* and *ermB*, could be identified by PCR and disk-diffusion methods, PCR methods were more reliable in elucidating these determinants. The susceptibility pattern to 14-, 15- and 16-membered macrolides and clindamycin differed between the $mefA^+$ and $ermB^+$ isolates (Kimura et al. 2003).

Pro. acnes and *Pro. granulosum* are widely regarded as the etiological agents of inflammatory acne. Their proliferation and metabolism are controlled by means of prolonged treatment with oral and/or topical antibiotics. The prevalence of skin colonization by antibiotic-resistant propionibacteria was tested among acne patients and their contacts from six European centers. A panel of tetracycline, macrolide, lincosamide and streptogramin B antibiotics was used in the tests. Viable propionibacteria were recovered from 622 patients. A total of 515 representative antibiotic-resistant isolates and 71 susceptible isolates acting as control strains were characterized phenotypically.

Resistant genotypes originally identified in the United Kingdom are distributed widely throughout Europe. Antibiotic-resistant propionibacteria can be considered transmissible between acne-prone individuals; and dermatologists should use strict cross-infection control measures when assessing acne in the clinic (Ross et al. 2003).

Effect on protozoa

Clindamycin has been successfully used for the treatment of infections caused by protozoa. It can serve as an antimalarial drug (Lell and Kremsner 2002) and was found effective in animals infected with chloroquine-resistant and sensitive *Pla. falciparum*. It is also effective against *Pla. vivax*, but not against the exo-erythrocytic parasites. In *Pla. falciparum*, clindamycin appears to be very effective in the cure of semi-immune subjects and increases quinine activity (Patenotte et al. 1995). Malaria caused by chloroquine-resistant strains can be successfully

treated with combinations of clindamycin with a classic antimalarial drug (Mordmuller et al. 1998).

Clindamycin is effective in experimental toxoplasmosis in mice. In cultured mammalian cells, clindamycin reduces the level of replication of *Tox. gondii*, affects the protein synthesis of free parasites and also impairs the ability of the parasite to infect host cells. Infections caused by *Tox. gondii* can be treated with clindamycin (Fung and Kirschenbaum 1996). Mutants of *Tox. gondii*, resistant to clindamycin, can be selected and these usually show cross-resistance to spiromycin and azithromycin (Fichera et al. 1995).

The influence of antimicrobial agents on the replication and stage conversion of *Tox. gondii* was described by Gross and Pohl (1996). Molecular genetic tools for the identification and analysis of drug targets in *Tox. gondii* were reviewed by Roos (1996).

Human babesiosis is an important emerging tick-borne disease. *Babesia divergens*, a parasite of cattle, has been implicated as the most common agent of human babesiosis in Europe and, with *Bab. microti*, is a common agent in the United States, causing severe disease in splenectomized individuals. Human babesiosis can be treated by clindamycin administered intravenously (Uguen et al. 1997). The current treatment for babesiosis focuses on a regimen of clindamycin and quinine (Kjemtrup and Conrad 2000). Lincomycin was also used as an inhibitor of protein synthesis in experiments concerning photoinactivation in plants and algae, as described by Sicora et al. (2003) and Kato et al. (2002).

Conclusion

Lincomycin and clindamycin are clinically important antibiotics. According to its worldwide production, the semisynthetic lincosamide derivative clindamycin belongs to the 20 most important antibiotic compounds. Lincomycin and clindamycin inhibit most Gram-positive bacteria, the genera *Staphylococcus* and *Streptococcus* in particular. They do not affect Gram-negative bacteria but exhibit a significant antibiotic activity against some anaerobic bacteria. They are therapeutically used, especially in cases when synergistic effects of a mixed anaerobic and aerobic microflora are anticipated (especially bone and articular infections, prevention of intra-abdominal infection after surgery, stomatological infections, anaerobic sepsis, skin and mucosa infections). Lincomycin and clindamycin are also a useful alternative to penicillin and its derivatives in the treatment of upper respiratory tract infections in patients with an allergy against penicillin. As compared with lincomycin, clindamycin is highly effective in the treatment of toxoplasmosis and pneumocystosis in AIDS patients. Clindamycin and some of its derivatives seem to be promising for the treatment of malaria caused by *Pla. falciparum*, even strains that have developed resistance to chloroquine, sulfonamides and pyrimethamine.

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