Topical Antibiotics

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Nowadays, topical antibiotics are the subject of much renewed interest and are being used on a wider scale than ever before. The reasons for using topical rather than oral therapy for a variety of dermatoses include direct application on Infected site, the higher achievable concentration of antibiotic at the site of action, reduced risk of systemic side effects, the avoidance of resistance selective in the gut microflora and the overall usage of less drug (1,2). The antibiotics which are toxic on systemic usage but nonabsorbable on topical application are preferred for topical usage (2). Several topical antibiotics are commercially available. Some of those that are commonly used are listed in Table I (3,4,5).

These preparations may be useful in the early treatment of superficial cutaneous wounds, impetigo and other superficial pyodermas and in the management of localized Infected eczema. Some of these are effective when used topically to treat acne vulgaris (1,4,6).

The selection of a particular antibiotic depends of course upon the diagnosis and, whenever possible, invitro culture and sensitivity studies of clinical samples. The pathogens isolated from most infected dermotoses are group A beta hemolytic streptococci, staphylococcus aureus or both (7,8). The pathogens present in the surgical wounds depend on the environmental information about regional epidemiologic data and the prevailing patterns of drug resistance is therefore important in selecting a therapeutic agent (7). Understanding the uses of topical antibiotics requires a knowledge of their antibacterial activity and activity spectrum, structure, mode of action, resistance mechanism and cross resistance with other antibiotics (9). Table II shows these features of some topical antibiotics (1).

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Some of these topical antibiotics cause a reactions. To avoid sensitisation, drugs should ***t*** plied for a short time and, to minimize further troi sensitisation does occur, the drug should be on will not be needed for systemic administration in (5).

POLYPEPTIDES

Antibiotics In this group are large cyclic pol tides with amino and carboxyl groups providing a face and hydrocarbon chains providing a non face. Thus, they act as cationic detergents, re; with the phosphate group of cell envelope phos pids. As a result, there is disorganization of the plasmlc membrane leakage of the intracellular coi and cell death. This effect is bactericidal. Since agents can affect mammalian cell membrane, esp ly in the renal tubule, they are used mainly to; for superficial infections (10, 11).

Polymyxins: Polymyxins, discovered in 194! elaborated by various strains of an aerobic spor ming rod, Bacillus polymyxia, which are found lr Only polymyxin B and E are available for clinical The activity of the polymyxins is related to a dete action on the bacterial cell membrane, resulting in of the organism (10,11). The action of polymy: markedly inhibited by purulent exudates (7).

Polymyxin B: Polymyxin B is effective ag gram-negative organisms, Including Pseudomona ruginosa, Escherichia coll, Enterobacter, Klebs Salmonella, Shigella, Pasteurella and Vibrio, strains of Proteus, Serretia species and Neisseria resistant to the drug, as are all gram-positive nisms (2,3,7,9,10). The topical preperations of myxin B are widely used because of its excellent vity against gram negative organisms but it is ha justify the use of polymyxin B topically for Pseud nas since Its activity Is promptly neutralised by dl\ cations found in body fluids (3,10). It is difflei achieve detectable serum concentrations with tc application, but the total daily dose applied to den skin or open wounds should not exceed 200 mg I

Table I. Most available topical antibiotics in clinical use

1 _ POLYPEPTIDES
- a. Polymyxin B
- b. Polymyxin E (Colistin)
- c. Basitracin
- d. Gramicidin

2. AMINOGLYCOSIDES
- a. Neomycin
- b. Gentamicin
- c. Framycetin

3. SULFONAMIDES
- a. Mafenide (Sulfamylon)
- b. Silver sulphadiazine

4. MACROUDES AND LYNCOSAMIDES
- a. Erytromydn
- b. Clindamycin

5. OTHER ANTIBIOTICS
- a. Tetracycline
- b. Chloramphenicol
- c. Novobiocin
- d. Nitrofrazon
- e. Fusidic acid
- f. Mupirocin

der to reduce the likelihood of neurotoxicity and phrotoxicity (7).

Polymyxin E (Colistin): Colistin Is also derive from species of Bacillus polymyxia, but is supplied the sulfomethl derivative (methanesulfonate) (10).

The polymyxins are also available in numer topical preparations such as ointments, creams, s tions, sprays and eye drops. They are combiner these preparations with other antibiotics such as r mycin and bacitracin (2,10).

Hypersensitivity to topical polymyxins is unc mon (7).

Bacitracin: This polypeptide antibiotic is isok from a strain rf Bacillus subtilis. Bacitracin is ac against gram-positive organisms. In addition, n anaerobic cocci, Neisserlae, Tetanus bacilli and phtheria bacilli are sensitive (3,7,10). All coliform b; li, Salmonella, Shigella, Proteus and Pseudomonas resistant (10). Bacitracin is poorly absorbed and systemic use may damage mammalian cells. For th **reasons its use is restricted to topical applicatioi**

Tablo II. Summary of currently available topical antibloitcs (1)

Antibiotic	Structure	Activity spectrum	Mode of action	Resistance mechanism	Sc re<
Neomycin (Famycetin)	Aminoglycoside	Broad spectrum not streptococ	Inh. of protein syn.	Inactivation	2,:
Gentamicin	Aminoglycoside	Broad spectrum	Inh. of protein syn.	Inactivation	2,:
Erythromycin	Macrolide	Gram (+) Neisseria and Haemophilus sp	Inhibition of protein synthesis	Efflux, modification of target, inactivation	1
Clindamycin	Lincosamide	Gram (+) and Grram (-) anaerobes	Inhibition of protein syn the si ss	Modification of target, inactivation	1
Tetracycline	Polyketlde	Broad spectrum	Inhibition of protein synthesis	Eff, modifie, of target, inactivation	1,:
Bacitracin	Dodecapeptide	Gram (+) and neisseria sp.	Inh. of cell wall syn.	?	3
Gramicidin	Cyclic decapeptide	Gram (+) only	Perturbation of cyt membr function	?	2,:
Polymyxin B	Branched cyclic decapeptide	Gram (-), not neisseria species	Perturbation of cyt membr function	?	3
Chloramphenicol		Broad spectrum	Inh. of protein syn	Inactivation reduced upt	1
Fusidic acid		Staph., corynebi neisseria	Inh. of protein synt	Modification, reduced upt	2,
Mupirocin (pseudomonic acid)		Gram (+) not propionibac. or corynebacteria	Inhibition of protein synthesis	Modifatlon of target	2,

1. Acne, 2. Primary skin Infect., 3. Secondary skin Infect., 4. Elimination of nasal carriage of S. aureus.

ointment form alone or In combination with neomycin, polymyxin B or both (7, 10). Unfortunately, it is not stable In water-miscible formulation and thus Is not a good choice when the occlusive properties of an ointment are undesirable (3).

Microbial resistance may develop following prolonged use. Badtracin-induced contact urticaria syndrome occurs rarely (7). Allergic contact dermatitis occurs more frequently (7, 12). Held J. et al reported two patients who developed allergic contact dermatitis due to bacitracin (13). It is poorly absorbed from the skin, so systemic toxicity is rare (7).

Gramicidin: Gramicidin Is a polypeptide antibiotic and available only for topical use In combination with other antibiotics such as neomycin, polymyxins, bacitracin and nystatin, as creams and ointments (5,7).

AMINOGLYCOSIDES

Aminoglycosides inhibit protein synthesis of a great deal of microorganisms irreversibly and show bactericidal effect (2,11).

Neomycin: Neomycin Is active against gram-negative organisms including E. coli, Proteus, Klebsiella and Enterobacter (7,14). Most staphylococci are sensitive to neomycin. Staphylococcus pyogenes is relatively resistant but at high concentrations these organisms are also probably killed by topical neomycin preparations. Neomycin in its various combinations is used more than its properties can justify (3). It Is commonly used topically In combination with other antibiotics in treatment of superficial pyodermas (10).

Neomycin frequently causes sensitization, particularly if used in to eczematous dermatoses or if compounded In an ointment vehicle or if used on chronically inflamed skin (3,7,8,15). When sensitization occurs, cross-sensitivity to streptomycin, kanamycin, paramomycin, bacitracin and gentamicin is possible (7,15). The risk of contact sentization is much reduced if neomycin is used for only 7 to 10 days. It should be avoided to use on the lower leg, especially in the presence of a venous ulcer (16). Neomycin cream is applied to burned skin and this can aggravate kidney damage caused by burn itself (17). The association of topical antibiotic resistance, particularly to neomycin and gentamicin is well documented. Aminoglycosides do not reach the surface of Intact skin in inhibitory amounts when administered orally. Therefore, it is not surprising that resistance emerged after the introduction of topical use (1).

Gentamicin: Gentamicin generally shows greater activity against Pseudomonas aeruginosa than neomycin. It is also more active against staphylococci and group A beta hemolytic streptococci (7). However, should not be applied topically as resistant strains pseudomonas, enterobacteria and staphylococci read emerge (5). In addition, widespread topical use of ge tamicin should be avoided to slow the appearance gentamicin-resistant organisms. Moreover, topical ge tamicin Is partly inactivated by purulent exudates (" Gentamicin if used excessively on large areas and skin ulcers, can be absorbed and cause system complications such as deafness (5,17). It is report* that gentamicin cream showed an excellent effect at rate of 55% and a moderate effect as 18% In patien with impetigo compared to placebo group (9).

FramycetIn: It contains 99% neomycin B, 1 neomycin C and 0.2% neamin. Its properties are sin lar to those of neomycin. Unlikely, hypersensitivi reactions of framycetin are uncommon (15).

SULFONAMIDES

Sulfonamides are structural analogs of p-amin benzoic acid (PABA). The action of sulfonamides bacteriostatic and reversible by removal of the drug In the presence of an excess of PABA. Sulfonamide can inhibit both gram-negative and gram-positive ba teria, Nocardia, Clamydia trachomatis and some prot zoa. In general, the application of sulfonamides to tr skin, in wound or on mucous membranes is undesir; ble because of their low activity and high risk of alle gic sensitization (7).

Mafenide (Sulfamylon): Mafenide acetate is use for prophylaxis of burn infections because of its wic antibacterial spectrum, including pseudomona (5,7,11). The drug is absorbed in 3 hours from the v< hide (7). Mafenide, absorbed from burned skin, ca make diuretic effect and cause hyperchloremic asidos by inhibiting carbonic anhydrase (11). Moreover causes significant pain on application (7,11). Applies tion form of mafenide for dermatitis is 2-5% ointmei and for burns 10% cream (2,11).

Silver sulfadiazine: It is made by substituting on molecule of silver for the ionizable hydrogen atom i sulfadiazine. It has been used widely for preventio and treatment of wound sepsis in patients with burn (3). The sulfadiazine is released slowly and low systt mic levels are seen. Care must be taken since hig sulfadiazine blood levels are found when silver suite diazine is applied to large areas. Silver sulfadiazin appears to be effective in controlling infecting flora < most burn wounds, especially if the burns are not to deep (7,11). Its antimicrobial effect is not inhibited b p-aminobenzoic acid or other metabolites that may b found in wounds or body fluids. It does not inhibit cai bonic anhydrase (11). This agent has many propertie

one would design into a first-aid cream and it deserves more extensive use (3). It is used as 1% cream (11).

MACROLIDES AND LYNCOSAMIDES

Erythromycine: It is isolated from streptomyces erythreus. Erythromycine shows bacteriostatic effect by preventing the protein synthesis in bacteria. Recently It is reported that erythromycine has also bactericidal effect on some microorganisms (1). Gram-positive microorganisms such as streptococci, some staphylococci, Corynebacterium diphteriae, Bacillus antracis, Clostridium species, Propionibacterium acne, and gram-negative microorganisms such as Neisseriae, Bordatella, Brucella, Haemophilus Influenza are sensitive to erythromycine.

In topical preparations, the base of erythromycine rather than the salt form is used to facilitate penetration. Although the mechanism of action of topical erytromycine In inflamatory acne vulgaris is unknown, it is presumed to be due to its inhibitory effects on P. acnes (7,9). Topical preparations of erythromycin may be clinically beneficis in mild to-moderate cases (1). Erythromycin 2% gel was compared with its vehicle in a double-blind study of patients with acne for 3 weeks. At the end of the study 60% of patients treated with erythromycin and of 36% treated with the vehicle had excellent results (18) A4 4% erythromycin and zinc combination lotion and a 2% erythromycin lotion were evaluated in a randomized, double-blind study in 122 patients with acne vulgaris. 4% lotion was more effective than 2%. This may have been due to a higher concentration of erythromycin or the zinc acetate complex may enhance the penetration of erythromycin into the skin (9). Aras N. et al. reported 40% Improvement in patients with acne vulgaris with 2% erythromycin (20).

One of the possible complications of the topical therapy Is the development of antibiotic resistant organisms including staphylococci (1,7,9). Adverse local reactions may include a burning sensation at the time of application and drying and irritation of the skin. Allergic hypersensitivity appears to be uncommon (7,5). Acute and delayed reactions are reported (15).

Clindamycin: Clindamycine is a semisynthetic antibiotic that is derivated from lincomycine. It is efective against most gram-positive microorganisms and some gram-negative anaerob pathogen microorganisms (11). Clindamycine has in vitro activity against P. acnes. This has been postulated as the mechanism of its beneficial effect in acne therapy (6,7,9). In addition, it has the effect of reducing free fatty acids and neutrophil Chemotaxis (8). Clindamycin, either phosphate or hydrochloride at 1% concentration is equal tc topical erythromycine in patients with acne vulgaris (9) Topical clindamycine (and erythromycine) was associated with the development of resistance in cuteneous propionibacteria (1). In a trial of clindamycine given foi 8 weeks, no resistant P. acnes emerged; resistant sta phylococci, however, became more common durinc therapy, but decreased after the medication was dis continued. In an other study clindamycine-resistant P acnes was isolated in 24% of patients who had recei ved topical clindamycine (9). Approximately 4-10% o an applied dose is absorbed and rare cases of blood' diarrhea and pseudomembranous colitis have been re ported following topical application (6,7,9,16). Clinda mycine phosphate is not absorbed from the skin, si antibiotic-associated colitis is not a risk (3,9). Tin hydroalcoholic vehicle may cause drying and irritatio of the skin, with complaints of burning and stinging Allergic contact dermatitis is uncomon (3,15).

OTHER ANTIBIOTICS

Tetracycline: Tetracyclines are broad-spectrur antibiotics that have bacteriostatic effect by Inhlbltln protein synthesis in ribozoms (11). Tetracyclines wei formerly the antibiotic of choice for many gram-positiv and gram-negative bacteria (21,22). Two topical tetr; cycline antibiotics are currently available for topic; treatment of acne vulgaris; 1- Tetracyclin hydrochloric in a hydroalcoholic base containin-decyl methyl si foxide and 2- Medocycline subsalicylate in a crea base (7). It is suggested that the activity of tetracyclir was not only linked to antimicrobial actions but also changes In sebum composition. It has been demostr ted that the administration of tetracycline causes a st king reduction in the concentration of the free fal acids In sebum without affecting the quantitative pr duction of sebum (7,21). Topical tetracycline hydr chloride was studied in a large number of subjec and compared with oral tetracycline hydrochloride ai plecebo. The results of this study indicated that topic tetracycline hydrochloride was as good as oral tetrac dine hydrochloride and better than placebo (23).

It does not commonly cause skin allergy but s! phylococci, which are common skin pathogens, are ten resistant to them (15,24). An inflammatory proce; myospherulosis, has recently been described and l ked to the topical application of tetracydine powder an oilbased ointment. Mooret al. and Eslaml et al. ported connective tissue reactions to 3% tetracycli ointment (24). In addition, Tetracydine can tempora color the skin yellow (6).

Novobiocin: Novobiocin is a gllcozlde antibic which is isolated from Streptomyces spheroides (11)

is a bacteriostatic reserve drug chiefly for treatment of resistant staphylococci. It has lost much of its importance since the introduction of beta-lactamase resistant penicillns (5,11).

Fucidlc asld (Sodium fusldate): It is a steroid antibiotic which is derivated from Fusidum coccineum. It inhibits protein synthesis and it has bacteriostatic effect (2,11). Its effective spectrum is narrow. Gram-positive and gram-negative cocci are sensitive. Most sensitive microorganism is staphylococcus aureus were (11,16). White et al. reported that 93% of patients healed (25). G. Gassels-Brown et al. found in their study that 69% of patients with impetigo, receiving sodium fusidate 2% ointment healed in 7 days (26). Sensitization reactions occur uncommonly. Ritchie found no cases of sensitization in his series of 12000 patients treated with topical sodium fucidate and this experience was repeated by Allen in a further 7000 cases (26). The development of fusidic acid resistance has been associated with topical use (1,2,16).

Nitrofurazone: Nitrofurazone is markedly bactericidal for many bacteria (7). It is used as a topical antimicrobial agent on superficial wounds or skin lesions and a surgical dressing. The preparation contains about 0.2% of active drug and does not interfere with wound healing (7,11). Howewer about 2% of patients may become sensitized and may develop reactions, e.g. acut generalized eruptions, contact dermatitis, allergic pneumonitis (7,15).

Cloramphenicol: Cloramphenicol was first isolated from cultures of streptomyces venesuelae. It is generally bacteriostatic but bacterisidal in some conditions. Cloramphenicol is effective against gram-positive and gram-negative microorganisms. It has topical preperations. Wound powders are of 2%, pomades are of 1% concentration (15,22). An improvement of 72.5% was reported with application of 1% cloramphenicol solution in patients with acne, at the end of 5 weeks. Irritation and desquamation due to topical application may be observed (19). Contact sensitivity reactions are uncommon and they acute urticaria and anaphylactic shock (15).

Muplrocln (Pseudomonic acid A): Mupirocin is a unique antibiotic compound produced by Pseudomonas fluorescens. It was formerly known as pseudomonic acid (5,7,8,9,27). Mupirocin blocks bacterial protein synthesis by binding reversibly to bacterial isoleucyl-t RNA synthase. This mechanism differs from those of other commonly used antibiotic and there is no cross resistance (6,8,11,28). It has excellent in vitro activity against staphylococci and most streptococci, but less activity against other gram-positive and most gram-negative bacteria with the exception of H. influenzae, N. meningitidis and N. gonorrhoeae (6, 9, 27,28). Unlike other topical antibiotics, mupirocin is effective for the treatment of impetigo caused by S. aureus. S. pyogenes, or other strains of streptococci and most tococci (6, 28).

After topical application, mupirocin is only ver nimally absorbed systernically (less than 1%) (6,2! Penetration into the deeper epidermal and de layers is enhanced in travmatised skin and unde elusive dressing. Mupirocin is slowly metabolise the skin to the antimicrobially inactive metabolite r acid (28,29). The therapeutic efficiency of mupi 2% ointment applied topically 2 or 3 times daily to 14 days has been documented in open and ve controlled studies in patients with primary skin i tions, and in secondary infection of dermatoses an jured tissue. In this study 80% of patients clinical!; red or markedly improved, and over 90% eradic of the bacterial pathogens was seen (28). White < showed that clinical efficency of mupirocin in the t ment of skin infections was excellent in 97% of tients (24). In a few studies, mupirocin has shown good potential for use in the eradication of S. aut including methicilin-resistant strains, from the ant nares of carriers (28). Dux et al. reported that 2% cal mupirocin was more effective in the present p lel-group study in resolving clinical sign and sympt of infection and in eliminating infecting bacilli thar ther systemic antibiotic, erytromycine or cloxacillin \ The results of another clinical open study suggest mupirocin is a topical antibiotic which is both safe effective in the treatment of skin infection with im vement of skin lesions in 75% of patients and bad eradication in 83.9%of cases (30). R.D. Wilkinson ported topical mupirocin to be efective and superio topical polymyxin B-neomycin compound in the tr ment of primary and secondary skin infections (; Two studies with 814 and 304 patients showed sig cant clinical advantage as 91% and 85% respectr (8). Local side effects such as burning, stinging ching and rash have been reported (25,28).

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