REVIEW ARTICLE

Drugs 2001; 61 (2): 175-185
0012-6667/01/0002-0175/$27.50/0

Comparative Review of Topical Ophthalmic Antibacterial Preparations

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Abstract

The choice of an antibacterial is based on considerations of pharmacodynamic, pharmacokinetic and bacteriological characteristics, risk of selecting resistant mutants, and cost. In this article we review 16 commercially available ophthalmic antibacterial preparations.

Fusidic acid and bacitracin are selective for Gram-positive bacteria whereas polymyxin B targets Gram-negative species. Aminoglycosides and quinolones are broad spectrum antibacterials. The widespread use of an antibacterial increases risks of selecting resistance to it. Acquired resistance is well documented for fusidic acid and rifamycin, and newly described for quinolones.

The bioavailability of an antibacterial agent depends on the target bacterial species, the site of infection and the integrity of the haemato-aqueous barrier.

Some agents (fusidic acid, quinolones) penetrate the cornea, passing into the anterior chamber of normal eyes at therapeutic concentrations, whereas others (polymixin B, bacitracin) have no penetrating powers and remain at the surface of the eye.

Toxicity is mostly manifested by allergic reactions to excipients or active ingredients in topical antibacterial preparations. A few cases of haematological toxicity have brought suspicion on topical chloramphenicol, but the link has yet to be proven. Erythromycin and polymyxin B are probably okay to use as topical applications in pregnant women and nursing mothers.

Costs of treatment must be evaluated as a whole (regimen, drug associations). Prices for a bottle of eyedrops may vary 3-fold. The cheapest drugs include chloramphenicol, polymyxin B and gentamicin, the most expensive being fusidic acid and the quinolones.

Treatment with antimicrobials must always aim to achieve effective concentrations at the specific site of infection. Choosing one (or more) appropriate antibacterial agents therefore implies consideration of their pharmacodynamic, pharmacokinetic and bacteriological properties, as well as sensitivity to mutant strains and overall cost. Ideally, the chosen antibacterial(s) should cover the entire spectrum of suspected bacteria, be cost effective and completely penetrate the infected site.

This article provides a review of all antibacterial preparations in current use, detailing their antibacterial mechanisms, spectrum of action, sensitivity to resistant strains, bioavailability and cost.

1. Antibacterial Effect

Choice of an antibacterial depends on the type of bacteria targeted, but must also take into consideration antibacterial mechanism, spectrum of action and effectiveness.

1.1 Mechanism of Action, Spectrum and Resistance

Specific mechanisms of action, spectrum of action and known cases of acquired resistance are listed below for each class of antibacterial agent.

- Aminoglycosides are polyoside antibacterial agents that inhibit ribosomal bacterial protein synthesis. They are bactericidal against a broad spectrum of bacteria including Gram-negative aerobes and Gram-positive cocci, including *Staphylococcus* species. However, *Streptococcus* species are frequently resistant,[1] which is possibly acquired through a plasmid transfer mechanism.[2]
- Second generation quinolones are small synthetic molecules that interfere with DNA and RNA synthesis by inhibition of bacterial DNA gyrase.[3] They are bactericidal against a broad spectrum of bacteria including some generally resistant species such as *Staphylococcus aureus* and *Pseudomonas aeruginosa*. Acquired resistance mechanisms are numerous: alteration of bacterial DNA gyrase, impaired drug permeation or enzymatic detoxification.[3,4]
- Fusidic acid has a sterol nucleus and is eliminated from the body via the bile. It inhibits bacterial protein synthesis, and is effective exclusively against Gram-positive cocci, especially *Staphylococcus* species. Fusidic acid is bacteriostatic but may be bactericidal at higher doses.[5] Gram-negative resistance is caused by membrane impermeability but acquired resistance within Gram-positive species is low.[5]
- Chloramphenicol is a small molecule, with a phenyl radical and four carbon atoms, that inhibits bacterial protein synthesis.[6] It is bacteriostatic, with a relatively broad spectrum against most Gram-positive and Gram-negative bacteria.[7] Relatively rare occurrences of acquired resistance seem to be caused by enzyme inactivation.[6]

- Tetracycline molecules are based around a common structure with 4 joined hexagonal nuclei. They inhibit bacterial protein synthesis, with a relatively broad spectrum covering most Gram-positive and Gram-negative bacteria. Tetracyclines display good intracellular penetration and are therefore used as a standard treatment for intracellular organisms (*Chlamydiae, Rickettsiae*). Resistant species are rarely encountered but the number of cases has been rising with the popularity of tetracyclines worldwide.[8] Cases of tetracycline-chloramphenicol cross-resistance have been suspected.[8]
- Rifamycin is a complex molecule that interferes with bacterial RNA synthesis. Its spectrum covers the *Mycobacteriae* and some Gram-positive bacteria, but is otherwise limited. Risk of acquired resistance is high.[7]
- Polymyxin B is a polypeptide of high molecular weight (approximately 1200 Da) that becomes fixed to the bacterial membrane. It is bactericidal against Gram-negative bacilli. Bacitracin has similar properties, except it is effective against Gram-positive bacteria only.[7]

Comparative spectra of activity for antibacterial agents available for topical application are reported in table I after Duval and Soussy,[7] ranging from drugs specific for one category of bacteria (e.g. polymyxin B, fusidic acid and rifamycin), to broad-spectrum antibiotics (e.g. chloramphenicol, aminoglycosides, tetracyclines, quinolones).

1.2 Acquired Resistance

Greater risk of acquired resistance to antibacterial agents occurs as their use increases, i.e. more bacteria come into contact with the antibacterial molecules. Fear of resistant bacteria may itself become a cause of increasing resistance with the physician feeling obliged to prescribe broad-spectrum antibiotics inappropriately (for prophylaxis, or treatment of benign or viral infections) to large numbers of patients, thereby increasing the risk of emerging resistance among bacteria.[9]

Four cases of keratitis with methicillin-resistant *S. aureus* also resistant to ciprofloxacin have been reported,[10,11] and the authors recommend limiting first-line use of ciprofloxacin to serious ocular infections as well as obtaining culture and sensitivity results before treatment.[10] Emerging resistance to ciprofloxacin mirrors its increasingly widespread systemic use.[11]

1.3 Bacteriological Efficacy Studies of Ophthalmic Preparations

Two comparative *in vitro* studies have been reported.[12,13] In 1995, Everett et al.[12] designed a comparative study of antibacterial sensitivity of bacterial isolates from conjunctivitis and blepharitis. This study showed that chloramphenicol (94% isolates susceptible) and bacitracin/polymyxinB (93%) constituted the most effective treatment,

Table I. Theoretical MIC_{90} (μg/ml) for *Staphylococcus aureus*, *Streptococcus pneumoniae*, *Escherichia coli* and *Pseudomonas aeruginosa*, according to Duval and Soussy[7]

	S. aureus	*S. pneumoniae*	*E. coli*	*P. aeruginosa*
Polymyxin B			0.5-2	2-8
Fusidic acid	0.03-0.16	2-16		
Rifamycin	0.01-0.1	0.01-0.1		
Chloramphenicol	3-12	1-8	3-12	16-32
Gentamicin	0.12-0.25	6-25	0.25-2	0.5-2
Tobramycin	0.12-0.5		0.25-1	0.25-2
Tetracycline	0.2-1	0.1-0.5	1-8	8
Norfloxacin	0.5-2	4-16	0.03-0.12	0.25-8
Ofloxacin	0.12-0.5	0.5-4	0.03-0.25	0.25-8
Ciprofloxacin	0.12-0.5	0.5-2	0.01-0.03	0.06-1

MIC_{90} = minimum inhibitory concentration.

Table II. Susceptibility of isolates from conjunctivitis (n = 385) and blepharitis (n = 173) to antimicrobial topical preparations, according to Everett[12]

Topical agent	Susceptible isolates (%)
Chloramphenicol	94
Bacitracin/polymyxin B	93
Ofloxacin	88
Sulfa drug[a]	87
Ciprofloxacin	85
Trimethoprim/polymyxin B	84
Norfloxacin	82
Gentamicin	80
Bacitracin	79
Trimethoprim	73
Tobramycin	70
Neomycin	67
Erythromycin	49
Polymyxin B	27

a Not specified.

whereas erythromycin (49%) and polymyxin B alone (29%) were the least effective (table II).

Osato et al.[13] in 1989 established the minimum inhibitory concentration (MIC_{90}) of several antibacterials against 3 major bacteria (*P. aeruginosa*, *S. aureus*, *Streptococcus epidermidis* and *S. pneumoniae*). Ofloxacin and norfloxacin had the lowest MIC_{90} for all 4 pathogens, and chloramphenicol and polymyxin B alone the highest (table III). The discrepancy between these 2 studies (for instance concerning chloramphenicol) is due to the relative rarity of the bacteria tested in Osato's study[13] (e.g. *S. Pneumoniae*, *P. Aeruginosa*) in bacterial isolates routinely isolated from conjunctivitis and blepharitis. Everett's study[12] provides interesting conclusions with regards to first-line treatment, although no measurement of MIC was made.

2. Kinetics

2.1 Pharmacodynamics Specific to Antibacterials

The aim of antibacterial therapy is to achieve a drug concentration at the infected site slightly superior to the MIC_{90} for bacteria presumed responsible for the infection. These considerations should be taken into account when choosing an antibacterial for 3 reasons. Firstly, required concentration is related to bacterial species. An antibacterial with poor intra-ocular penetration may still achieve sufficient concentrations when used against bacteria for which it has a low MIC_{90}. Secondly, bioavailability of an antibiotic must be considered with regard to the site of infection: conjunctivitis or superficial keratitis may be treated with drugs with low intra-ocular penetration, whereas corneal abscesses require drugs with good corneal-penetration and, in endophthalmitis, antibacterials that achieve therapeutic concentration in both the vitreous and aqueous humors are required. Thirdly, the infectious condition itself may influence drug bioavailability: intra-ocular penetration can increase by a factor 10 to 40 if the corneal epithelium is injured or if the hemato-aqueous barrier is impaired; alternatively, infections can occur in regions where drug accessibility is low, e.g. in deep corneal abscesses, the periphery of haptics or behind implants. Therefore, the use of antibacterial agents needs to be adapted accordingly.

Table III. MIC_{90} (μg/ml) for *Pseudomonas aeruginosa*, *Staphylococcus aureus*, *Streptococcus epidermidis* and *S. pneumoniae*, as reported by Osato[13]

	P. aeruginosa (n = 68)	*S. aureus* (n = 79)	*S. epidermidis* (n = 68)	*S. pneumoniae* (n = 21)
Ofloxacin	4	0.5	0.5	2
Norfloxacin	4	2	2	14.4
Gentamicin	8	1	32	7
Tobramycin	4.4	2	64	16
Chloramphenicol	128	16	32	4
Polymyxin B	32	>128	>128	>128

MIC_{90} = minimum inhibitory concentration.

Pharmacological *in vivo* studies are numerous and extremely variable, with frequency of administration, time between last dose and sample as well as experimental conditions differing from a study to another. Consequently, results quoted here must be understood as being merely indicative of possible concentrations.

2.2 Kinetics of Available Topical Antibacterials

2.2.1 Quinolones

Four agents are currently available as topical preparations: norfloxacin, ofloxacin, ciprofloxacin and levofloxacin. The first 3 agents have been studied on a large scale with respect to intra-ocular penetration.

Norfloxavin

Bron et al.[14,15] established in rabbits that norfloxacin concentration was 14.3 ± 3.7 mg/g, 3.3 ± 0.7 mg/g and 0.2 ± 0.1 mg/ml, respectively, in cornea, conjunctiva and aqueous humor 30 minutes after instillation of 1 drop of norfloxacin 0.3% (n = 20). After removal of the corneal epithelium, these concentrations rose to 84.2 ± 15.8 mg/g, 7.3 ± 2.3 mg/g, 8.6 ± 1.9 mg/ml, respectively. Mean intracorneal concentration 15 minutes after instillation was 15.5 ± 2.1 mg/g.

Diamond et al.[16] found intracorneal norfloxacin concentrations of 0.54 mg/g in 12 keratoplasty patients, after 4 instillations of 0.3% drops. According to these data, one may consider that after topical instillation, the intracorneal concentration of norfloxacin reaches at least 15 mg/g in the normal eye, and over 80 mg/g after epithelial abrasion.

Studies on intracameral penetration of norfloxacin in the human eye are numerous. Behrens-Baumann[17] reported in 19 patients aqueous concentrations between 0.014 and 0.105 mg/ml in normal eyes, and up to 0.206 mg/ml in one eye with neovascular glaucoma. Leeming et al.[18] reported an intracameral concentration of 0.14 mg/ml after 1 drop per hour for 6 hours. Donnenfeld et al.[19] reported concentrations of 0.057 mg/ml (n = 32), Huber-Spitzy et al.[20] 0.60 ± 0.38 mg/ml (n = 46) and Akkan et al.[21] concentrations as high as 2.95 ± 1.19 mg/ml (n = 30), after 1 drop per hour for 6 hours.

Concentrations of norfloxacin in the aqueous humor vary between 0.1 to 3 mg/ml, in other words higher than the MIC_{90} of most Gram-negative bacilli, but lower than the MIC_{90} of some Gram-positive cocci, especially *Streptococcus*.[7]

Norfloxacin 0.3% is undetected in serum 3 hours after instillation into the human eye.[22]

Ofloxacin

As for norfloxacin, penetration of ofloxacin into the anterior chamber has been widely examined. In rabbits, intraocular concentration peaks at 11.4 mg/ml (aqueous) and 0.026 mg/ml (vitreous)[23] 1 hour after topical application of ofloxacin 0.3%. Diamond et al.[16] reported intracorneal ofloxacin concentrations of 0.81 mg/g after administration of 0.3% drops to 12 patients.

Donnenfeld et al.[19] found a concentration of 0.338 mg/ml in aqueous humor after the instillation of 2 drops of 0.3% 90 and 30 minutes before sampling in 32 patients. Luthardt et al.[24] detected 0.56 ± 0.37 mg/l (n = 40) after 1 drop every 15 minute for 2 hours. Durmaz et al.[25] detected 0.964 ± 0.693 mg/ml after 1 drop every 15 minutes beginning 90 minutes before sampling (n = 30) and Akkan et al.[21] 1.50 ± 0.48 mg/ml in aqueous humor after 1 drop per hour for 6 hours. The intracameral concentration of ofloxacin can reach 5.55 ± 2.53 mg/ml (n = 21) when using antibacterial-soaked soft contact lenses.[24]

Corneal and aqueous humor concentrations of ofloxacin of at least 0.3 mg/ml, sometimes 1.5 mg/ml, can be attained, concentrations that are bactericidal for most bacilli.

Ciprofloxacin

Diamond et al.[16] demonstrated intracorneal concentrations of ciprofloxacin up to 0.60 mg/g with 0.3% drops. McDermott et al.[26] observed variable concentrations of ciprofloxacin within the cornea (5.28 ± 3.4 mg/g) after instillation of 0.3% eyedrops. According to the manufacturer's prescribing information, ciprofloxacin corneal concentrations are 5 mg/g after 1 drop of 0.3% per hour for 10 hours, 173 mg/g after 1 drop per 15 minutes

for 4 hours, and 900 mg/g after corneal abrasion.[22]

Studies on the intracameral penetration of ciprofloxacin have produced extremely variable results: Donnenfeld et al.[19] reported concentrations of 0.072 mg/ml, with 2 drops 90 and 30 minutes before sampling, Durmaz et al.[25] 0.092 ± 0.077 mg/ml after 1 drop every 15 minutes for 90 minutes, Leeming et al.[18] 0.22 mg/ml after 1 drop hourly. Cekic et al.[27] found 0.36 mg/ml in the aqueous humor and 0.21 mg/ml in the vitreous after 2 drops every 30 minutes for 3 hours and then hourly over 3 hours. Luthardt et al.[24] found 0.38 ± 0.33 mg/ml (n = 38) with topical instillation and 1.16 ± 0.61 mg/ml with ciprofloxacin-soaked soft contact lenses, and Akkan et al.[21] 2.80 ± 1.07 mg/ml after 1 drop of 0.3% per hour for 6 hours (n = 30).

The concentration of ciprofloxacin reaches 16 mg/ml in tear fluid 4 hours after 1 drop applied to healthy volunteers, 2.6 mg/ml in serum after 2 drops per hour in corneal ulcer, and 2.4 mg/ml in serum after 2 drops every 4 hours in conjunctivitis.[22]

The intracameral and intracorneal concentrations of ciprofloxacin achieved are high enough to be effective against most organisms, since the MIC_{90} for ciprofloxacin is generally less than 1 mg/ml except for bacteria such as *Bacteroides fragilis*, and some species of *Staphylococcus* and *Streptococcus*.

Levofloxacin

A fourth quinolone (levofloxacin) was introduced in the US in 2000. Levofloxavin penetrates the anterior chamber up to 1.90 ± 0.97 mg/L 12 hours after oral administration of 2.5g tablets (study in 23 patients with cataracts),[28] but pharmacokinetic data after eyedrop instillation are still unpublished. Experimental studies on isolated rabbit cornea show that transportation of levofloxacin through the cornea is carrier-mediated, reaches a maximum value at pH = 6.5[29] and is mainly mediated in the epithelium.[30]

2.2.2 Aminoglycosides

Aminoglycosides applied topically are known to be poor diffusers, but compelling evidence in the literature indicates that they penetrate the anterior chamber – even though this may be at infra-therapeutic concentrations.

Gentamicin

According to manufacturer's figures, gentamicin concentrations are below 0.2 mg/ml in aqueous humor when the cornea is intact.[22] Peyman et al.,[31] comparing intra-ocular penetration of gentamicin in the phakic and aphakic eye, demonstrated that vitreous humor concentrations of injected gentamicin barely exceeded the bactericidal threshold and that levels rapidly subsided after 1.5 hours. He concluded that intra-ocular injection was necessary to achieve an intra-ocular bactericidal concentration of gentamicin. Nontherapeutic levels of gentamicin occur in the aqueous humor after topical instillation,[32] but if the corneal epithelium is injured, concentrations reach 32 mg/ml in aqueous humor 1 hour after 1 drop per 15 minutes of gentamicin 2%.[33] In a recent study, Luthardt et al.[24] demonstrated therapeutical intracameral concentrations of gentamicin (2.08 ± 4.63 mg/ml, n = 24) after 1 drop every 15 minutes for 2 hours, and even higher concentrations when using soft contact lenses as a drug delivery system (3.41 ± 4.77 mg/ml, n = 29).

Tobramycin

Osher et al.[34] was unable to detect tobramycin diffusion into the anterior chamber in humans. Durmaz et al.[25] also failed to detect tobramycin in the aqueous humor after at least 90 minutes of topical application of 1 drop of tobramycin every 15 minutes (n = 30). However, collagen shields may increase tobramycin penetration and produced concentrations of up to 6.48 mg/ml.[35] Luthardt et al.[24] reported concentrations in the anterior chamber of 0.49 ± 0.79 mg/l after topical instillation (n = 22), and 1.09 ±1.30 mg/ml when using tobramycin-soaked soft contact lenses.

Serum concentrations after the application of tobramycin eyedrops are low. Filatov et al.[36] recorded plasma concentrations of less than 0.2 mg/ml after 1 drop every half hour in a patient with renal failure and in a 3 month-old infant.

2.2.3 Fusidic Acid

Fusidic acid is available as a 1% microcrystalline emulsion eyedrop preparation. In this form it achieves fair penetration into the anterior chamber: concentrations of 0.3 mg/ml have been detected in the anterior chamber after a unique instillation of fusidic acid eyedrops even after 12 hours, and concentrations as high as 0.8 mg/ml have been reached after repetitive doses.[37] The currently recommended regimen (2 instillations a day) produces concentrations equal or superior to those reached after systemic administration. These concentrations are above the MIC_{90} of fusidic acid for most sensitive bacteria, especially *Staphylococcus* species.

The biological half-life of fusidic acid after instillation of eyedrops has been assessed by Thorn and Johansen[38] to be 7.3 hours.

2.2.4 Chloramphenicol

Using rabbits, Aldana et al.[39] found concentrations of topical 0.5% chloramphenicol in the aqueous humor reached a peak at 0.11 mg/ml 45 minutes after instillation. Plasma concentrations were more than 1000 times lower that those observed after intravenous administration. Ocular bioavailability was 16.2% and total bioavailability was 34.0%.

In 1979, Trope et al.[40] detected no systemic chloramphenicol after topical instillation (n = 5).

Given its small molecular weight and liposolubility, chloramphenicol penetrates the anterior chamber, but not always at therapeutic concentrations.

2.2.5 Other Antibacterial Agents

Topical rifamycin achieves therapeutic concentrations in the anterior chamber in rabbits, at doses effective against Mycobacteria.[41]

5% vancomycin eyedrops reach the anterior chamber in rabbits, at concentrations of up to 16 mg/l.[42] However, topical vancomycin is not available other than as fortified eyedrops.

2.2.6 Drugs Not Reaching the Anterior Chamber

Osher et al.[34] showed that trimethoprim 0.1%/polymyxin B 10 000 units/ml failed to achieve intracameral bacterial inhibitory levels after topical instillation. Intra-ocular penetration of polymyxin B is impossible because of its high molecular weight.

Framycetin is unable to penetrate the eye because it is not lipid soluble.[22]

Micronomicin crosses the cornea to a very small extent. However, if the cornea is physically damaged, concentrations in aqueous humor of 32 mg/ml may be achieved 1 hour after instillation of 1 drop of micronomicin 2% every 15 minutes.[22]

3. Toxicity

3.1 Allergy

Allergy to active substances or preservatives may be the cause of persistent conjunctival irritation during treatment for bacterial conjunctivitis. Using a set of 15 substances for hypersensitivity testing, Rudzki et al.[43] demonstrated allergic reactions in 35% of 97 patients, especially for neomycin, gentamicin, thiomersal, and benzalkonium chloride. Hatinen et al.[44] reported allergic reactions in 44.4% of 27 patients with chronic conjunctivitis, noting reactions particularly to neomycin (18.5%), bacitracin (7.4%) and benzalkonium chloride (3.7%).

3.2 Drug Toxicity

Petrousos et al.[45] demonstrated that corneal epithelialisation was inhibited by high doses of bacitracin (10 000 units/ml), gentamicin (10 mg/ml) and neomycin (8 mg/ml) whereas lower doses (respectively, 500 units/ml, 3 mg/ml and 3.5 mg/ml) caused no delay in epithelial healing.

The aminoglycoside toxicity study group[46] has reported macular infarction, even discrete, with intravitreal injections of amikacin sulfate 0.2 to 0.4mg or gentamicin 0.1 to 0.2mg, demonstrating that retinal toxicity of aminoglycosides is possible even when low-dose regimens are employed.

No retinal toxicity, as measured clinically, by electroretinogram and histologically, was noted in rabbits after instillation of ofloxacin 0.3% every 30 minutes for 8 hours a day over a 4-week period.[23]

Pseudomembranous conjunctivitis has been reported following topical gentamicin therapy.[47]

3.3 Statement on Topical Chloramphenicol Toxicity

Chloramphenicol is a low priced, broad-spectrum antibacterial agent with little evidence of bacterial resistance.[48] It was consequently adopted worldwide as a first-line treatment for a broad range of infections until in the early 1980s its potential haematotoxicity, even with eyedrop delivery, began to be suspected.[49,50] Since then, chloramphenicol use has reduced drastically in the US, while continuing to be prescribed on a relatively large scale in the UK.[51] Controversy over chloramphenicol eyedrops has generated an abundance of literature during the last 4 years.[48,51-59]

The first case of fatal aplastic anaemia following administration of topical chloramphenicol was reported by Fraunfelder et al.[50] in 1982. Seven cases were subsequently described.[48,50,60] Epidemiological data are available in 3 retrospective studies. Hall et al.[54] reported 11 haematological reactions, all nonfatal, among 200 million doses dispensed in the UK during the same period (1966-1995). Lancaster et al.[61] reported 3 cases of serious hematotoxicity and 1 case of mild leucopenia among 442 543 patients (674 148 prescriptions). Finally, Fraunfelder et al.[62] reported 23 cases of blood dyscrasias associated with topical chloramphenicol between 1982 and 1984.

The annual incidence of aplastic anaemia in the general population is 3 per million patients,[55] of which the cause remains unknown in up to 50% of cases. Possible causal agents are multiple in individual patients and the aetiology of aplastic anaemia often relies on presumption rather than certainty. Therefore, every risk factor has to be evaluated using epidemiological statistics.

Aplastic anaemia is a well known adverse effect of systemic chloramphenicol in 1 out of 50 000 patients.[63] The debate on the haematological toxicity of chloramphenicol eyedrops involves toxicological, pharmacological, statistical and economic considerations.

Chloramphenicol may induce medullar aplasia in 2 ways. The principal mechanism is a reversible, dose-dependent suppression of medullar precursors.[63] Another more serious mechanism, which occurs in approximately 1 in 50 000 cases, involves idiosyncratic, irreversible pancytopenia leading to fatal medullar aplasia. This latter effect is neither dose- nor time-dependent and, therefore, a single dose may be responsible for death. No study has yet shown whether chloramphenicol eyedrops can produce systemic levels high enough to initiate myelotoxicity.

Being among the cheapest antibacterial agents, chloramphenicol has been widely adopted throughout the world and is prescribed most of the time by non-ophthalmologists. Economic considerations are consequently an important aspect of the chloramphenicol eyedrops controversy.

Finally, only a controlled study could prove the relationship between a drug and an adverse effect. In the case of chloramphenicol eyedrops, such a study would not be without difficulties. First, the aetiology of aplastic anaemia is always hard to establish with certainty: 50% of cases remain of unknown aetiology, and every risk factor (especially toxic) has to be evaluated in terms of exposure (duration, delay before aplasia). Secondly, patients are not systematically required to take eyedrops. These considerations apply to the few cases of supposed hematotoxicity described at the start of this section. When comparing available data, the incidence of aplastic anaemia seems even lower in patients treated with chloramphenicol eyedrops (Lancaster et al.:[61] 3 patients in 442 543 patients in 7 years) than in the general population (3 per 1 000 000 per year).

Two pitfalls must be avoided in this question: on the one hand, not investigating a possible fatal adverse effect and, on the other hand, taking account of fortuitous associations in a small number of patients. At the present time, on available evidence, systemic toxicity of chloramphenicol eyedrops still remains to be proven. We look forward to the results of the UK aplastic anaemia study,[53] a 4-year, multicentre, case-control study which should provide solid scientific data on this subject.

3.4 Pregnancy and Lactation

Guidelines for the prescription of topical antibiotics in pregnant women are based on toxicity data for systemically administrated drugs. In a comparative review in 1988, Samples and Meyer[64] gave the following recommendations.

- Erythromycin and polymyxin B seem 'safe' and may be prescribed.
- Systemic aminoglycosides cause fetal ototoxicity. In animal experiments, rifampicin (rifampin) has been linked with a higher rate of neonatal malformations (spina bifida, anencephaly and cleft palate). However, fetal complications after topical administration of these drugs in pregnant mothers have as yet not been described. Thus, aminoglycoside and rifamycin eyedrops should be prescribed with care.
- Systemic chloramphenicol administration in mothers during the late stages of pregnancy causes neonatal gray syndrome: vomiting, cyanosis, flaccidity. Tetracyclines cause primary teeth discoloration in pregnant mothers and may cause malformation of bone extremities. These agents should therefore be avoided in pregnancy.

4. Costs

4.1 Comparative Costs of Topical Antibacterials

Topical antibacterials available in France in 1999 are listed in table IV. Gentamicin, chloramphenicol, oxytetracycline and kanamycin/polymyxin B are the cheapest preparations, whereas rifamycin, fusidic acid and quinolones are the most expensive.[22] Costs given are the price of one bottle of eyedrops, and/or one tube of ointment, representing at most 15 days of treatment.

The overall cost of treatment may be higher for various reasons, including prolonged medication, increased frequency of application to improve bioavailability, use of combinations of drugs to broaden the spectrum. Clinical studies are required to determine whether the use of expensive broad-spectrum agents which have intra-ocular penetration instead of cheaper targeted surface molecules makes treatment less or more expensive in the long term.

4.2 Treatment of Trachoma

Economic considerations are one of the main barriers stopping early treatment of trachoma and preventing blindness around the world. Standard therapy involves topical medicine (oxytetracycline/

Table IV. Ophthalmological antibacterial preparations available in France in 1999[22]

Agent	Formulation		Preservative (drops)	Price (French francs)	
				drops	ointment
Gentamicin	D,O	0.3%	Benzalkonium	11.00	11.00
Kanamycin + polymyxin B	O	2.6mg + 5200 UI/dose	None		11.40
Chloramphenicol	D	0.4%	Methyl parahydroxybenzoate	12.20	
Gentamicin	D,O	0.3%	Benzalkonium	14.20	13.70
Oxytetracycline	D,O	1%	Polyvidone, trometamol	16.70	12.50
Neomycin	D	3500 UI/ml	None	16.80	
Bacitracin	D	500 UI/ml	None	17.20	
Micronomicin	D,O	0.3%	Benzalkonium	18.40	15.50
Tobramycin	D,O	3000 UI/ml	Benzalkonium	18.50	18.50
Neomycin + polymyxin B	D,O	3400 UI+10 000 UI/ml	Edetate	19.40	13.00
Framycetin	D	1%	Borate phenylmercure	19.60	
Rifamycin	D,O	1%	Polyvidone, mercurothiolate	22.40	17.70
Norfloxacin	D	0.3%	Benzalkonium, edetate	22.60	
Ofloxacin	D	0.3%	Benzalkonium	25.20	
Fusidic Acid	S	1%	Benzalkonium, edetate		26.50
Ciprofloxacin	D	0.3%	Benzalkonium, edetate	35.50	

D = drops; **O** = ointment; **S** = suspension.

polymyxin B), general treatment (oral azithromycin) and surgery for sequellae.

In a global evaluation of the Trachoma Control Program in Burma between 1964 and 1994, Evans et al.[65] evaluated the cost of tetracycline 0.1% treatment for trachoma at $US11 for each handicap-adjusted life year and $US163 for each case of visual impairment prevented.

5. Conclusions

Sixteen types of antibacterial drugs were available in 2000 to treat ocular infection via a topical route. Some have a good intra-ocular penetration (fusidic acid, quinolones), others remain surface antibiotics (polymyxin B, bacitracin). Some have a selective effect (polymyxin B, fusidic acid, bacitracin), others a broad spectrum (chloramphenicol, aminoglycosides, tetracyclines, quinolones). Some are cheap (chloramphenicol, polymyxin B, gentamicin), others expensive (fusidic acid, quinolones).

Prescribing topical antibacterial agents must take account of all these factors so that the antibacterial used is correctly adapted to the target bacteria, therapeutic concentrations can be achieved at the site of infection, risks of selecting resistant mutants and drug toxicity are minimised while drug prices are also kept low. The best way is probably to prescribe the cheap targeted surface-acting agents whenever possible, and to reserve expensive broad-range, intra-ocular penetrating agents for severe infections.

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