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Treatment of Acute Bacterial Conjunctivitis With Topical Netilmicin

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Purpose. This study compares the clinical and microbiologic value of topical netilmicin with that of gentamicin in the treatment of acute bacterial conjunctivitis. **Methods.** A double-blind, randomized, prospective, controlled study was performed in 209 patients. One to two drop(s) of either antibiotic was applied to the affected eye(s) four times a day for up to 10 days. Patients were examined at the time of diagnosis and after 3, 5, and 10 days. Clinical efficacy was measured as the cumulative sum score (CSS) of the key signs and symptoms of acute bacterial ocular infection. Sensitivity/resistance was evaluated using the disk diffusion method. **Results.** Drug efficacy assessment was restricted only to patients with positive baseline culture results ($n = 121$). Of the isolated organisms, 96.9% were sensitive to netilmicin, whereas only 75.0% were sensitive to gentamicin ($p = 0.00001$). Netilmicin provided a broad-spectrum coverage comparable with that of ciprofloxacin, ofloxacin, and norfloxacin. Netilmicin also was more effective than gentamicin in eradicating infections ($p = 0.001$ at day 5 and $p = 0.037$ at day 10) and in ameliorating the CSS ($p = 0.037$ at day 3, $p = 0.001$ at both day 5 and day 10). Only minor adverse events occurred in patients treated with either netilmicin or gentamicin. **Conclusions.** This study demonstrates that netilmicin is a safe and effective antibiotic that can be used as first-line therapy for the treatment of acute bacterial conjunctivitis.
Key Words: Conjunctivitis—Antibiotic resistance—Aminoglycosides—Netilmicin.

Conjunctivitis and blepharitis are common external ocular infections that ophthalmologists confront frequently. Although bacterial conjunctivitis usually is considered to be self-limiting, if left untreated it may develop into a more serious, sight-threatening condition.

External ocular infections caused by gram-positive organisms progressively increased during the last decade and account at present for approximately 90% of these infections. The most common causative agents for external ocular infections are *Staphylococcus aureus* and *Staphylococcus epidermidis*,[1,2] although the specific causal organisms are frequently unknown. In fact, bacterial cultures are not routinely done for several reasons, including cost, time necessary to obtain results, and high percentage of negative cultures.[3] Therefore it is important that the initial therapeutic plan offers the best expectation for rapid eradication of the suspected pathogen. For these reasons, ocular infections usually are treated with topical broad-spectrum antibacterial drugs.

The multitude of available broad-spectrum antibiotics raises questions about the most appropriate drug to use today. First, no single antibiotic or combination product available is able to provide 100% coverage against all isolates.[1] In addition, in vitro studies indicate that many of the established older compounds are just as effective in the eradication of ocular infections as the newer antibiotics (such as fluoroquinolones).[1] Finally, use (and overuse) of the most recent agents has allowed many bacterial species to develop resistant strains. Accordingly, the number of reports of fluoroquinolone resistance for both gram-positive and gram-negative ocular bacterial isolates has increased.[4,5] Thus, these new antimicrobials probably should be reserved for the treatment of vision-threatening conditions, like keratitis, whereas the established antibiotics should be considered for the treatment of uncomplicated conjunctivitis.

First-generation aminoglycosides, such as gentamicin and tobramycin, are widely prescribed as first-line therapy for the treatment of external ocular infections.[6–8] However, approximately 20–30% of isolates usually are resistant to these compounds.[1,9,10] The more recent aminoglycoside netilmicin has been shown to be active in vitro against isolates resistant to gentamicin and tobramycin.[11–13] Netilmicin ophthalmic solution (Nettacin; SIFI SpA, Catania, Italy) shows excellent activity against the most common microorganism involved in ocular infections[14] and is able to cross the cornea of rabbits, reaching aqueous humor levels comparable with the minimal inhibitory concentration for usual ocular pathogens.[15] In addition, netilmicin ophthalmic solution is able rapidly to resolve clinical signs and symptoms and to eradicate the causative organisms of ocular infection with a resistance rate much lower than that of tobramycin.[16]

The current double-blind clinical study was designed to confirm the value of topical netilmicin treatment in patients with acute bacterial conjunctivitis.

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Netilmicin ophthalmic solution (Nettacin) is manufactured by SIFI SpA.

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MATERIALS AND METHODS

A total of 209 patients of either sex, at least 3 years of age and with suspected acute bacterial conjunctivitis (signs and symptoms of acute bacterial infection such as conjunctival hyperemia, itching, burning, foreign body sensation, secretion, tearing, eyelid redness, eyelid edema, presence of scars), were enrolled at five study sites in Italy (Messina, Turin, Rome, Catania, and Venice). A washout period of 72 hours was required for those patients who had previously been treated with other topical or systemic antibiotics. Exclusion criteria included known or suspected allergy to aminoglycosides, contact lens wear, concomitant ocular medications, and use of systemic antibiotics, corticosteroids, and immunosuppressive agents. The local ethics committees approved the study protocol. All patients gave written informed consent. All patients gave written informed consent according to the Declaration of Helsinki.

Patients were randomly assigned to receive either 0.3% netilmicin ($n = 106$) or 0.3% gentamicin ($n = 103$). One to two drops of either netilmicin or gentamicin was applied to the affected eyes four times daily until resolution and up to 10 days. Every night, approximately 1 cm of either netilmicin or gentamicin ointment also was applied to the affected eyes. The study was designed as prospective, randomized, double-blind, active-controlled, parallel-group study.

At the time of diagnosis (baseline evaluation), medical and ophthalmic histories were taken, visual acuity tested, biomicroscopy and ophthalmoscopy performed, symptoms of ocular infection assessed, and conjunctival specimens obtained. The conjunctival swab was performed with the patient looking up as the swab was wiped twice across the lower conjunctival cul-de-sac from the temporal to the nasal margin.

The conjunctival swabs were immediately transported to the closest microbiology facility by using Mini-Tip Culturette (Becton Dickinson, Milan, Italy) with a modified Stuart's bacterial transport medium. Swabs were streaked onto the surface of selective media. The elapsed time between collection of the culture specimens and plating of the swab in the laboratory did not exceed 4 hours. Plates were then shipped to the reference microbiology laboratory (Pharmaco-Biological Department, University of Messina) for pathogen characterization (Api System, Biomerieux, Rome, Italy) and sensitivity testing. Sensitivity testing was performed according to the Kirby-Bauer disk diffusion method by using disks (Oxoid, Milan, Italy) for susceptibility assays (netilmicin 30 μg, gentamicin 10 μg, ofloxacin 5 μg, ciprofloxacin 5 μg, and norfloxacin 10 μg).

The patients were reexamined on days 3 and 5 and, eventually, also on day 10. If the infection was eradicated at day 5, the treatment was stopped and the patient discontinued. Follow-up examinations consisted of the same clinical observations as the baseline examinations and also included an assessment of the patient's comfort with the drug treatment. Bacterial cultures of the conjunctival specimens were performed at days 5 and 10.

Evaluation was based on both efficacy and safety criteria. Drug efficacy assessment was restricted to patients with positive baseline culture results (efficacy subset), based on the criteria of Cagle and Abshire.[7] All patients enrolled were evaluated for drug safety (*safety subset*).

The end point of the study was the clinical resolution of ocular infection as assessed by either clinical or microbiologic parameters.

Clinical efficacy was measured as the cumulative sum score (CSS) of several signs and symptoms of acute bacterial ocular infection (palpebral redness, palpebral edema, presence of scares, conjunctival hyperemia, conjunctival edema, itching, burning, foreign body sensation, pain, secretion, and tearing). Each sign and symptom was recorded using a four-point scale: 0 = none, 1 = mild, 2 = moderate, and 3 = severe. At the end of the trial the clinical outcome was evaluated as follows: resolved (CSS = 0); improved (CSS < baseline and > 0); unaltered (CSS = baseline and >0); or worsened (CSS > baseline or patient discontinued because of lack of drug efficacy).

Microbiologic efficacy was determined by evaluating changes from the baseline in bacterial colony counts. Microbiologic outcomes, based on the worst outcome of all species at all culture sites, were classified as proliferated (bacterial colony count positive, based on species-specific criteria listed previously and greater than baseline); no change (bacterial colony count equal to baseline); reduced (bacterial colony count less than baseline but still greater than the species-specific threshold listed previously); controlled (bacterial colony count less than the species-specific threshold listed previously); or eradicated (bacterial colony count equals zero).

The safety of the treatments was evaluated by noting adverse reactions and any change from the baseline evaluation. Comfort of the test medications was scored as 1 (not tolerated), 2 (mildly tolerated), 3 (tolerated), or 4 (well tolerated) at the end of the treatment period.

Categorical data were analyzed with frequency tables and treatments were compared with the χ^2 method. The methods used to discriminate among means were the Student *t* test and the Fisher's least significant difference procedure.

RESULTS

Microbiologic Results

Of the 209 enrolled subjects, 121 (57.8%) had positive baseline cultures. One hundred twenty of these 121 subjects were adults (age, 49 ± 19 years, mean ± SD). Fifty-five culture-positive subjects received gentamicin and 66 netilmicin. Because in seven cultures more than one species of bacteria was isolated, the total number of isolates was 128. Gram-positive organisms accounted for 89% of bacterial isolates, whereas gram-negative organisms were recovered in 11% of isolates. The most frequent gram-positive isolates recovered were *S. epidermidis* (45% of cases) and *S. aureus* (37%).

All isolates were screened for sensitivity/resistance against netilmicin, gentamicin, ofloxacin, ciprofloxacin, and norfloxacin. A list of all species and their antibiotic susceptibilities is given in Table 1.

Netilmicin provided broader-spectrum coverage than gentamicin (96.9% susceptibility vs. 75.0%, respectively; $p = 0.00001$, χ^2 test). The cumulative susceptibility of gram-positive organisms was 99.1% for netilmicin and 75.4% for gentamicin, whereas the susceptibility of gram-negative organisms was 78.6% and 71.4%, respectively (Table 1). Netilmicin resistance was observed in three gram-negative (*Pasteurella pneumotropica, Acinetobacter lwoffi, Pseudomonas aeruginosa*) and 1 gram-positive strain (*S. epidermidis*). All netilmicin-resistant strains also were gentamicin resistant. On the other hand, 28 of the 32 gentamicin-resistant strains were netilmicin sensitive (Table 2).

TABLE 1. *List of species isolates and their antibiotic profiles*

	Gentamicine			Netilmicin			Ciprofloxacin			Norfloxacin			Ofloxacin			
	S	I	R	S	I	R	S	I	R	S	I	R	S	I	R	Total
Gram positive																
S. aureus	38	1	3	40	2	0	39	3	0	42	0	0	42	0	0	42
S. epidermidis	25	3	23	50	0	1	48	0	3	47	1	3	48	0	3	51
Coagulase-negative staphylococci	16	0	2	17	1	0	17	1	0	17	1	0	18	0	0	18
Micrococcus sp	2	0	0	2	0	0	2	0	0	2	0	0	2	0	0	2
Streptococcus sp	1	0	0	1	0	0	1	0	0	1	0	0	1	0	0	1
Total gram positive	82	4	28	110	3	1	107	4	3	109	2	3	111	0	3	114
(%)	71.9	3.5	24.6	96.5	2.6	0.9	93.8	3.9	2.3	95.6	1.8	2.6	97.4	0	2.6	100
Gram negative																
Acinetobacter sp	3	0	1	3	0	1	4	0	0	4	0	0	4	0	0	4
P. aeruginosa	2	0	1	2	0	1	3	0	0	3	0	0	2	1	0	3
Serratia sp	2	0	0	2	0	0	2	0	0	2	0	0	2	0	0	2
Pasteurella sp	0	0	2	1	0	1	2	0	0	2	0	0	2	0	0	2
Haemophilus sp	2	0	0	2	0	0	2	0	0	2	0	0	2	0	0	2
Neisseria sp	1	0	0	1	0	0	1	0	0	1	0	0	1	0	0	1
Total gram negative	10	0	4	11	0	3	14	0	0	14	0	0	13	1	0	14
(%)	71.4	0	28.6	78.6	0	21.4	100	0	0	100	0	0	92.8	7.2	0	100
Gram positive + gram negative	92	4	32	121	3	4	121	4	3	123	2	3	124	1	3	128
(%)	71.9	3.1	25.0	94.6	2.3	3.1	94.6	3.1	2.3	96.1	1.6	2.3	96.9	0.8	2.3	100

Data are expressed as number of isolates (% of total in parentheses).
R indicates resistant; S, sensitive; I, intermediate.

The cumulative susceptibility of microorganisms to netilmicin was comparable with that to fluoroquinolones (96.9% vs.97.7%, respectively; Table 1). Netilmicin showed the lowest resistance rate for gram-positive organisms (<1%), whereas no gram-negative organisms were resistant to fluoroquinolones (Table 1). The strains resistant to ofloxacin, ciprofloxacin, and norfloxacin were all *S. epidermidis* (all sensitive to netilmicin and not to gentamicin).

As shown in Fig. 1, netilmicin was more effective than gentamicin in increasing the percentage of eradicated infections over time. These differences were statistically significant (day 5: $p = 0.001$, χ^2 test; day 10: $p = 0.037$).

Clinical Results

Drug efficacy was restricted to patients with positive baseline culture results ($n = 121$, efficacy subset). A rapid clinical improvement was observed in almost all patients. However, in accordance with the microbiologic results, netilmicin was more effective than gentamicin in ameliorating clinical symptoms as assessed by CSS mean values (Fig. 2). These differences were statistically significant for visits on all days (day 3: $p = 0.037$, Student t test; day 5: $p = 0.001$; day 10: $p = 0.001$). In addition, the percentage of patients with CSS = 0 (resolved clinical outcome) was significantly higher in the netilmicin group at both day 5 ($p = 0.01$, χ^2 test) and at day 10 ($p = 0.001$; Table 3).

Patients treated with netilmicin discontinued the treatment after 5 days in a higher percentage of cases compared with those treated with gentamicin (62.1% vs. 30.4%; $p = 0.0005$, χ^2 test). Accordingly, the length of exposure in the netilmicin group was lower than that in the gentamicin group (6.9 ± 2.4 vs. 8.1 ± 2.4 days, mean ± SD; $p = 0.0004$, Student t test).

TABLE 2. *Cross-resistance of isolated bacterial strains to netilmicin and gentamicin*

		Gentamicin		
		Sensitive	Resistant	Total
Netilmicin	Sensitive	96	28	124* (96.9)
	Resistant	0	4	4* (3.1)
Total		96* (75.0)	32* (25.0)	128 (100)

Data are expressed as number of isolates (percentage of total in parentheses).
* $\chi^2 = 23.53$, $p = 0.00001$.

Safety and Tolerance

Safety and tolerance were analyzed in all 209 randomized subjects (safety subset). Adverse reactions to drug treatment were encountered in 2 of the 106 patients treated with netilmicin (1.9%) and in 4 of the 103 treated with gentamicin (3.9%). None of these

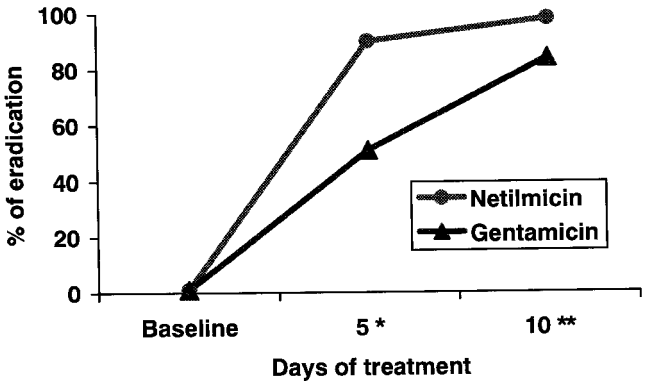

FIG. 1. Effect of netilmicin and gentamicin on the microbiologic eradication of infections. Conjunctival specimens were obtained during the first visit (baseline examination). Sensitivity testing of the clinical isolates for netilmicin and gentamicin was performed according to the Kirby-Bauer disk diffusion method. Bacterial cultures were repeated at day 5 and, if necessary, at day 10. Microbiologic efficacy was determined by evaluating changes from the baseline in bacterial colony counts. The figure shows the percentage of patients (over total, $n = 121$) whose infections were eradicated (bacterial colony count = 0). *$\chi^2 = 18.55$, $p = 0.001$; **$\chi^2 = 7.84$, $p = 0.037$.

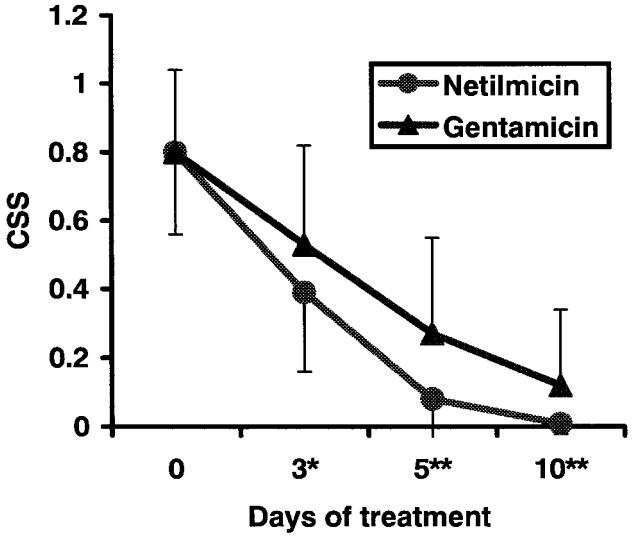

FIG. 2. Effect of netilmicin and gentamicin on CSS score. Symptoms and signs of ocular infection were assessed at baseline, day 3, day 5, and, if necessary, at day 10. Clinical efficacy was assessed using the CSS. Data are expressed as means ± SD (n = 121). Student t test: *p = 0.037, **p = 0.001, ***p = 0.001.

events was serious or required hospitalization. The side effects observed with both treatments included redness, itching, and burning. A complete recovery was observed in all cases.

Treatment tolerance was rated as excellent or good in a higher percentage of patients belonging to the netilmicin group compared with those in the gentamicin group (96.9% vs. 70.9%), but this difference was not statistically significant.

DISCUSSION

The last 20 years have seen the emergence of gram-positive microorganisms as major pathogens in external ocular infections. In general, the current study confirmed previous data in which gram-positive bacteria predominated as the etiologic agents of conjunctivitis and blepharitis.[1,2] However, the specific causal organisms usually are unknown because microbiologic and susceptibility tests are time consuming, expensive, and often negative.[3] This finding was confirmed in our study as well because only approximately 60% of patients had abnormal swab cultures. For these reasons, external ocular infections usually are treated on an empirical basis with topical broad-spectrum antibacterial drugs.[3] Under these circumstances, it is not surprising that bacteria frequently develop resistance to commonly used antibiotics. An example is the fluoroquinolones, highly active, broad-spectrum antibiotics with many uses in both human and veterinary infections. Fluoroquinolones have become one of the most prescribed antibiotics for treating external ocular infections. However, as expected, the number of reports of fluoroquinolone resistance for both gram-positive and gram-negative ocular bacterial isolates recently has increased.[4,5] Therefore, to retain the excellent activity of this class of antibiotics and reduce the development of resistant strains and their spread, fluoroquinolones should be used prudently and only where there is a clinical need. For these reasons, in most ocular infections it has been suggested that fluoroquinolones not necessarily be considered as first-line agents[17] and that they should be reserved for treatment of more serious conditions. In addition, in vitro studies indicate that many of the established older compounds, such as aminoglycosides, are just as effective in the eradication of ocular infections as the fluoroquinolones.[1,2] Moreover, Alexandrakis et al. have recently reported a threefold increase in the percentage of *S. aureus* resistant to fluoroquinolones from 1990 to 1998, whereas in the same period the overall laboratory resistance to aminoglycosides has remained approximately stable.[4]

Netilmicin is a recently developed, semisynthetic aminoglycoside antibiotic that has been shown to be active in vitro against isolates resistant to gentamicin and tobramycin.[11–13,18] Netilmicin ophthalmic solution has excellent activity against the microorganisms most frequently isolated from ocular infections.[14] In addition, netilmicin eye drops are capable of rapidly resolving clinical signs and symptoms and eradicating the causative organisms of ocular infection.[16] The data obtained in this double-blind, multicenter trial confirmed that netilmicin is well tolerated and showed a high degree of clinical efficacy in the treatment of acute bacterial conjunctivitis, significantly reducing clinical signs and symptoms within 3 days. In addition, several parameters evaluated during the study indicate that netilmicin acts better and faster than gentamicin in ameliorating clinical symptoms. The treatment was well tolerated by most of the patients; the incidence of side effects attributed to netilmicin was low (approximately 2%), and none of them was serious.

Although resistance based on in vitro testing may not reflect true clinical resistance, in vitro susceptibility testing is the only established method of determining antibiotic resistance. In this study, the overall susceptibility of all bacteria to netilmicin was 97%, compared with 75% for gentamicin. Cumulative susceptibilities were 99% (netilmicin) and 75% (gentamicin) for gram-positive organisms and 79% (netilmicin) and 71% (gentamicin) for gram-negative organisms. The observed global resistance rate to netilmicin (3.1%) was comparable with that to fluoroquinolones (2.3%), suggesting that netilmicin provides a spectrum of coverage comparable with that of ofloxacin, ciprofloxacin, and norfloxacin.[1,5,19]

In conclusion, the current study indicates that netilmicin is safe, effective, and well tolerated in the treatment of acute bacterial conjunctivitis. In addition, netilmicin offers excellent broad-spectrum coverage against all the isolates (especially gram-positive), suggesting that it can be effectively used as a first-line agent in the treatment of such infections.

TABLE 3. *Clinical outcome*

Day	Treatment	Clinical outcome				Total
		Resolved	Improved	Unaltered	Worsened	
3	Gentamicin	0	47 (85.5)	2 (3.6)	6 (10.9)	55 (100)
	Netilmicin	0	65 (98.5)	1 1.5	0	66 (100)
5	Gentamicin	11* (20.0)	42* (76.4)	1 (1.8)	1 (1.8)	55 (100)
	Netilmicin	36* (54.5)	30* (45.4)	0	0	66 (100)
10	Gentamicin	31† (56.4)	22† (40.0)	1 (1.8)	1 (1.8)	55 (100)
	Netilmicin	62† (93.9)	4† (6.1)	0	0	66 (100)

Data are expressed as number of patients (percentage of total in parentheses).

* χ^2 = 14.61, p = 0.01.

† χ^2 = 22.17, p = 0.001.

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