

# Controlled multicenter study on chronic suppurative otitis media treated with topical applications of ciprofloxacin 0.2% solution in single-dose containers or combination of polymyxin B, neomycin, and hydrocortisone suspension

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Otic drops of either ciprofloxacin 0.2% solution (CIP) or a combination of polymyxin B, neomycin, and hydrocortisone suspension (PNH) were administered for 6 to 12 days to patients (14-71 years old) with chronic suppurative otitis media in a randomized, nonblinded, multicenter clinical trial. Two hundred thirty-two enrolled patients were analyzed for efficacy on a "per protocol" basis. The most frequently identified causal agents were *Staphylococcus aureus* (28% of the patients), *Pseudomonas aeruginosa* (19%), and *Staphylococcus sp* (9%). Clinical success was observed in 91% and 87% of the CIP- and PNH-treated patients, respectively. At 1-month follow-up, 4% of CIP and 6% of PNH patients showed a relapse of otorrhea. Bacteriologic eradication was seen in 89% and 85% of patients in the CIP and PNH groups, respectively. At 1-month follow-up, reinfection or recurrence of infection appeared in 3 patients in the PNH group and in 1 patient in the CIP group. Both treatments were well tolerated. The most frequently reported adverse events were pruritus, stinging, and earache. Audiometric tests did not show changes attributable to study drugs in any but 1 patient in the PNH group. This clinical trial shows that topical 0.2% ciprofloxacin solution in single-dose containers is effective and well tolerated in patients with chronic suppurative otitis media. (Otolaryngol Head Neck Surg 2000;123:617-23.)

**I**n chronic suppurative otitis media (CSOM), antibacterial therapy for persistent or recurrent episodes of otorrhea

still raises questions concerning the antibiotic choice, adequate route of administration and regimen, and adverse reactions to drugs. Because *Pseudomonas aeruginosa*, *Staphylococcus aureus*, gram-negative bacilli, and anaerobic organisms, alone or in combination, are the predominant source of infection,<sup>1,2</sup> it is important to rely on medications with a broad spectrum of activity because identification and susceptibility tests cannot always be performed on a routine basis in daily practice.

Management of CSOM with ototopical agents is common practice among otolaryngologists. Several combinations of topical otic preparations are available to treat external and middle ear infections. They remain the cornerstone of treatment, despite the fact that some of them are recognized as ototoxic drugs, and convincing evidence of sensorineural hearing loss in animals has been found.<sup>3</sup> The major components of these drops include polymyxin B, neomycin, gentamicin, or chloramphenicol, to which a corticosteroid is frequently added. In Spain an otic suspension of polymyxin B, neomycin, and hydrocortisone (Otosporin) is available and broadly used, and was subsequently selected as the reference treatment in our clinical trial. This combination is also available in most of the European countries and also in the United States, where it is the most frequently used ototopical treatment by otolaryngologists.<sup>4</sup>

Ciprofloxacin, a synthetic fluoroquinolone administered by oral route, is associated with high bacteriologic and clinical response rates,<sup>5-7</sup> because of both its satisfactory penetration in the middle ear and its broad spectrum of antibacterial activity. In noncontrolled clinical experiences, ototopical ciprofloxacin at concentrations as low as 0.2% has provided higher percentages of clinical and bacteriologic cures, which are not optimized through simultaneous administration of oral ciprofloxacin.<sup>8,9</sup> No evidence of ototoxicity after topical application of ciprofloxacin has been previously seen in animal<sup>3,10,11</sup> or clinical<sup>5-9,12-14</sup> studies. Ciprofloxacin could not be detected in plasma after otic applications, suggesting the absence of systemic absorption.<sup>13</sup> Therefore the availability of a topical antibiotic preparation with an appropriate antimicrobial spectrum and without the risk of ototoxicity would be a valuable addition to the therapeutic management of middle ear infections. Furthermore, the

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availability of a sterile and preservative-free formula supplied in single-dose containers for application to the middle ear also represents an achievement according to the European Pharmacopoeia specifications.<sup>15</sup>

The objective of this clinical trial was to compare the efficacy and safety of a newly developed sterile and preservative-free formula of ciprofloxacin 0.2% solution supplied in single-dose containers versus a combination of polymyxin B, neomycin, and hydrocortisone suspension (Otosporin), both of which were applied topically in patients with CSOM.

## METHODS AND MATERIAL

This prospective, randomized, open, comparative, multicenter clinical trial was designed according to the European Guidelines on evaluation of antibacterial medicinal products.<sup>16</sup> ENT physicians from 16 centers in Spain conducted the study. Ethics committees from each center as well as the Spanish Health Authorities reviewed and approved the study protocol. Participants received detailed information on the study, including a patient information sheet, and their written consent was obtained before enrollment.

To be included in the study, patients of either sex, 14 to 71 years old and capable of following the investigator's instructions, had to have CSOM defined as serous, mucous, mucopurulent, or purulent otorrhea; a history of persistent tympanic perforation or the presence of a tympanostomy tube along with the current episode lasting for at least 6 weeks; and bacteriologic confirmation of ear infection. Patients presenting with mucopurulent or purulent discharge were enrolled, irrespective of the culture results. Subjects with persistent ear infection despite topical or systemic antibacterial therapy could be enrolled after a 72-hour washout period. The exclusion criteria were as follows: acute otitis externa, fungal otitis, otorrhea associated with the presence of cholesteatoma, presence of severe otalgia or fever greater than 38°C, infection requiring systemic therapy, participation in another clinical trial in the previous 30 days, contraindication to the study drugs, pregnancy or suspected pregnancy and absence of contraceptive measures.

Patients were randomly allocated to study treatments: ciprofloxacin sterile and preservative-free 0.2% solution, supplied in 0.5-mL single-dose containers (Laboratorios Vita, SA, and Química Farmacéutica Bayer, SA), 0.5 mL twice daily for 10 days (valid interval 6-12 days); or polymyxin B sulfate, neomycin, and hydrocortisone suspension, supplied in multiple-dose containers (Otosporin; Gayoso Wellcome, SA), 3 drops (0.15 mL) 4 times daily for 10 days (valid interval 6-12 days). No other treatment for CSOM was permitted. Compliance with the study medications was checked by counting the number of CIP single-dose containers or the volume of PNH left in the multiple-dose containers returned to the investigators on visit 2. Because of different dosing schedules (0.5 mL twice daily vs 0.15 mL 4 times daily), packaging (single-

dose vs multiple-dose containers), and galenic form (solution vs suspension), a double-blind design had to be discarded. The limited capacity of the external auditory canal precluded the use of the double-dummy technique.

Patients were examined by the investigators on 3 occasions: on the day of enrollment (baseline, or visit 1), 2 to 7 days after the end of treatment (visit 2), and 1 month later (visit 3). At visit 1, a thorough ENT examination was done, a sample of the ear discharge was taken, and an audiometric assessment was performed. All patients received aural toilet by microscopic examination and were instructed about the application of study treatments. They were advised to apply the medication in a supine position with the target ear facing the ceiling. One single-dose container (0.5 mL) of CIP or 3 drops (0.15 mL) of PNH were to be introduced into the external meatus at each application. The tragus was to be massaged repeatedly, and the same position was maintained for 5 minutes. This procedure was to be repeated twice a day for CIP treatment and 4 times a day for PNH treatment. At visit 2, the efficacy of treatments was assessed based on the presence or absence of otorrhea. A sample of ear discharge (if present) was taken for microbiologic culture. Only patients who were cured were appointed to visit 3, where ENT examination and audiometric tests were repeated. If ear discharge was present, a sample for culture was taken.

Bacteriologic tests were carried out at each participating center. Specimens of discharge obtained by the investigators were inoculated into appropriate agar media (eg, blood, MacConkey) and identified after incubation with standard microbiologic techniques. Sensitivity to ciprofloxacin, polymyxin B, and neomycin was tested using the disk method.

Audiometric assessment was done by the investigators at each participating center and consisted of pure-tone audiometry for air- and bone-conduction hearing. Frequencies between 250 and 8000 Hz (air hearing) and between 250 and 4000 Hz (bone conduction) were measured and recorded on the audiogram.

The primary variable of efficacy was clinical response at visit 2 and was defined as follows: cure, absence of otorrhea or presence of serous/mucous otorrhea with negative microbiologic culture; and failure, presence of purulent or mucopurulent otorrhea irrespective of culture results or presence of serous/mucous otorrhea with positive culture. Dropouts due to lack of efficacy after at least 3 days of treatment or due to adverse events were also classified as therapeutic failures. Dropouts resulting from any other cause were classified as not evaluable.

The secondary variables of efficacy were clinical response at visit 3 and bacteriologic outcome at visits 2 and 3. Clinical response at visit 3 was defined as sustained cure (absence of otorrhea or presence of serous/mucous otorrhea with negative culture) or relapse (reappearance of purulent or mucopurulent otorrhea irrespective of culture results or serous/mucous otorrhea with positive culture). Bacteriologic outcome at visit 2 was defined according to the following definitions: eradication, the

causative organism of the infection was eliminated in the post-treatment culture, and no new organism was identified; presumed eradication, culture could not be done because of the absence of ear discharge; persistence, at the end of treatment the culture was positive, with isolation of the same pathogen responsible for the infection; superinfection, a new pathogen was identified as being responsible for the infection; and indeterminate, baseline cultures were negative or not done, or no cultures were obtained at the end of therapy despite positive cultures at baseline. At visit 3, bacteriologic outcome was defined as eradication or presumed eradication (absence of the organism in the repeated culture 1 month after treatment or culture could not be done because of the absence of otorrhea), recurrence (reappearance of the pathogen eradicated or presumably eradicated at the end of treatment), reinfection (isolation of a new pathogen different from the organism eradicated or presumed eradicated at the end of treatment), or indeterminate (absence of the organism in repeated cultures or no cultures performed).

Safety assessment was performed by recording all adverse events observed and reported by participants during the study period. The study coordinator (N.M.) blindly reviewed all pretreatment and posttreatment audiograms to identify any ototoxicity evidence arising from the treatments. Furthermore, to evaluate the potential systemic absorption of topically applied ciprofloxacin, researchers in one center (H. General de Vic), in agreement with the informed consent form, drew a 10-mL blood sample from the patients 1 to 2 hours after the first dosing. Plasma samples were kept frozen at  $-20^{\circ}\text{C}$  and sent to Bayer AG (a pharmacokinetic laboratory in Wuppertal, Germany), where plasma levels of ciprofloxacin were assayed by means of a validated high-performance liquid chromatography method. The lower limit of detection was set at  $10\ \mu\text{g/L}$ .

At each patient visit, the investigators entered the data using a personal computer (IBM ThinkPad) supplied with a validated software program (RDES SL), including an electronic study-specific case report form, interactive instructions for use, as well as checks for selection criteria compliance, treatment schedules, inconsistencies, and out-of-range and absent values. Data were transmitted each month by study monitors (Phoenix International Life Sciences Spain) to a central database for final review, data cleaning, and final statistical analysis.

The study was designed as an equivalence clinical trial to demonstrate the null hypothesis that CIP is not therapeutically inferior to PNH (unilateral equivalence analysis), assuming a maximum difference in clinical cure rates between the treatments equal to or lower than 15%. The sample size was estimated to be 360 randomized patients (180 per treatment group). Power curves were obtained for this sample size according to the formulas of Machin and Campbell.<sup>17</sup> This sample size ensures a power of at least 80% in any case of observed cure rates of at least 65% and rates of valid patients not higher than 30%. The confirmatory statistical analysis was performed on the “per protocol” population of patients. The

**Table 1.** Study populations

Study population	CIP	PNH	Total
Randomized patients	168 (52%)	154 (48%)	322
Safety analysis*	165 (52%)	153 (48%)	318
Evaluable patients†	155 (53%)	138 (47%)	293
Per protocol‡	119 (51%)	113 (49%)	232

\*Patients having received at least 1 dose of either study treatment.

†Patients with clinically/bacteriologically proven CSOM and evaluated at visit 2 after a minimum of 3 days of treatment, or less than 3 days in the case of treatment withdrawal due to adverse events.

‡Patients fully compliant with protocol specifications or treatment failure after 4 days of treatment.

90% confidence interval (2 sided) for the observed difference in clinical cure rates between the two treatments was calculated by means of the odds ratio-adjusted Mantel-Haenzsel test. As a secondary statistical analysis, the same approach was performed on the “evaluable patients” population and the “randomized patients” population. A descriptive statistical analysis was carried out on the pretreatment and posttreatment data. Qualitative variables were expressed by the number and percentages of patients in each category. Continuous variables for each group of patients were analyzed in terms of mean, standard deviation, and median, minimum, and maximum values.

## RESULTS

### Study Population

Between February 1996 and May 1997, 328 patients from 16 sites were enrolled in the study, and 322 of them were randomly allocated to study treatments (6 patients were not randomized because of protocol violations). Four randomized patients did not receive any dosing (3 in the CIP group and 1 in the PNH group), so the safety analysis was based on the 318 patients who received at least 1 dose of the study treatment. Of the 322 randomized patients, 29 were not evaluable for efficacy at visit 2 (13 in the CIP group and 16 in the PNH group), as a consequence of loss to follow-up (10 cases), fungal otitis (7 cases), or bacteriologic tests not performed (12 cases). Finally, the evaluable population consisted of 293 patients. Sixty-one evaluable patients were considered invalid as “per protocol” because of violations concerning either visit schedules (32 cases), treatment compliance (27), duration of therapy (20), randomization error (3), concomitant prohibited therapy (2), or presence of cholesteatoma (2). Therefore the final population of valid per protocol patients on which primary efficacy analysis was performed consisted of 232 patients (119 in the CIP group and 113 in the PNH group). The study populations are shown in Table 1. Unless otherwise stated, all the results given below refer to the per protocol population of patients.

**Table 2.** Baseline and initial evaluation characteristics

Characteristics	CIP (n = 119)	PNH (n = 113)
Males [n (%)]	79 (66)	63 (56)
Age in years [median (range)]	44 (14-70)	45 (14-71)
Years since first symptoms of CSOM [median (range)]	7 (0-58)	6 (0-56)
No. of episodes of otorrhea during the previous year* [median (range)]	3 (1-20)	3 (1-12)
Months since last episode [median (range)]	3 (1-14)	3 (1-13)
Patients treated during the previous episode [n (%)]	54 (45)	49 (43)
Patients with previous ear surgery [n (%)]	42 (35)	37 (33)
Ear infection [n (%)]		
Unilateral	111 (93)	102 (90)
Bilateral	8 (7)	11 (10)
Discharge [n (%)]		
Purulent	61 (51)	60 (53)
Mucopurulent	48 (40)	35 (31)
Mucous	7 (6)	12 (11)
Serous	3 (3)	6 (5)
Causal pathogens [n (%)]		
<i>S aureus</i>	33 (28)	31 (27)
<i>P aeruginosa</i>	24 (20)	20 (18)
<i>Staphylococcus</i> sp	13 (11)	8 (7)
Others <sup>†</sup>	46	44
Days of evolution of current episode [median (range)]	15 (1-180)	15 (1-365)

\*Including the current episode.

<sup>†</sup>No percentage per patient group is given because more than 1 pathogen could be isolated per subject. Other pathogens isolated were *Klebsiella* sp (5), *Serratia* sp (4), *Pseudomonas* sp (2), *Escherichia* sp (8), *Proteus* sp (13), other *Enterobacteriaceae* (16), *Haemophilus* sp (4), other gram-negative bacilli (8), *Streptococcus* sp (5), *Corynebacterium* sp (15), and other pathogens (10).

**Table 3.** Analysis of clinical responses at visit 2 (primary efficacy variable)

Patient population (n)	Cure rates (% (+/n))		Observed difference in cure rates	90% CI of the difference
	PNH	CIP		
Per protocol (232)	87% (98/113)	91% (108/119)	-4%	-8.86% to 4.48%
Evaluable patients (293)	81% (112/138)	90% (140/155)	-9%	-12.89% to -1.93%
Randomized patients (322)	76% (117/154)	87% (146/168)	-11%	-16.43% to -5.21%

### Baseline Evaluation

No difference was seen between the two treatment groups as far as baseline and initial evaluation characteristics are concerned (Table 2). Time elapsed since the first episode of otitis extended from less than 1 year to 58 years, and the total number of episodes during the previous year ranged from 1 to 20. In most patients, 3 months had elapsed since the last episode, although the interval was longer than 1 year in some cases.

About half of the patients had received some treatment during the last episode of otorrhea (dexamethasone, 40 cases; ciprofloxacin, 21 cases; boricated alcohol, 13 cases; fluocinolone acetonide, 12 cases; amoxicillin, 8 cases). Approximately one third of the patients had previously undergone extensive ear surgery.

Enrollment took place after a median otorrhea development of 15 days (range 1-365 days). About 90% of the patients had a unilateral ear affected. The most fre-

quently observed symptoms were hypoacusia (95%), tinnitus (30%), otalgia (25%), vertigo (14%), and cephalgia (14%). Tympanic perforation was present in all cases, and discharge was purulent or mucopurulent in 91% of CIP patients and 84% of PNH patients.

Cultures were positive in 92% of patients in the CIP group (111/119) and in 91% of patients in the PNH group (103/113); 19 patients with purulent or mucopurulent discharge had negative cultures. Of the 278 micro-organisms isolated from bacteriologic cultures (140 CIP, 138 PNH), 219 were considered as the causal pathogen of the infection (116 CIP, 103 PNH). The most prevailing causal pathogens were *S aureus* (28%), *P aeruginosa* (19%), and *Staphylococcus* sp (9%). Susceptibility tests showed that 84% of the causal pathogens were sensitive to ciprofloxacin (84% CIP, 83% PNH) and 78% were sensitive to polymyxin B and/or neomycin (80% CIP, 76% PNH).

No statistical difference was observed between evaluable and per protocol patients with respect to baseline parameters or pretreatment microbiologic results.

### Treatment Compliance and Duration

All the patients were fully compliant with the treatment and received at least 80% and no more than 100% of the prescribed doses. The median duration of therapy was 10 days (7-12 days) in both treatment groups.

### Clinical and Bacteriologic Efficacy

**Clinical results.** In the per protocol population, 108 of 119 (91%) patients in the CIP group and 98 of 113 (87%) patients in the PNH group were cured at visit 2 (Table 3). The 90% confidence interval of the observed difference in clinical cure rates between PNH and CIP (-4%) yielded a lower limit of -8.86% and an upper limit of 4.8%, both of which were below the maximum value of 15% that defined therapeutic equivalence.

In the evaluable patients and the randomized patients, the percentages of subjects classified as cured at visit 2 were also slightly higher in the CIP group (90% and 87%, respectively) than in the PNH group (81% and 76%, respectively). Lower and upper limits of the 90% confidence intervals of the observed differences in clinical cure rates were also below the maximum value of 15%.

At the third visit, 1 month after the end of treatment, 78% of patients in both the CIP and PNH groups had sustained cure, 17% of patients (18% in the CIP group, 16% in the PNH group) did not attend the follow-up visit, and 5% of patients (4% in the CIP group and 6% in the PNH group) showed a relapse of otorrhea.

**Bacteriologic results.** With respect to the bacteriologic response at visit 2 (Table 4), the performance of microbiologic culture was not always possible, in general as a consequence of the absence of otorrhea (76% in both treatment groups) and to a lesser extent for other reasons (eg, culture not done, culture not evaluable). The rate of eradication (including presumed eradication) was 79% in the CIP group and 76% in the PNH group. The bacteriologic outcome was classified as indeterminate in 38 patients (20 in the CIP group and 18 in the PNH group). Of these, 14 in the CIP group and 12 in the PNH group were clinically cured at visit 2, but the bacteriologic outcome was indeterminate because either baseline cultures were negative or not done or no cultures were obtained at the end of therapy despite positive cultures at baseline. Excluding these patients, the rate of eradication (including presumed eradication) at visit 2 was 89% in the CIP group and 85% in the PNH group. Infection persisted in 8 patients, 1 in the CIP group (*Staphylococcus epidermidis*) and 7 in the PNH group (*P aeruginosa* [2], *Proteus mirabilis*, *S aureus*,

**Table 4.** Bacteriologic outcome at visits 2 and 3

Bacteriologic outcome	CIP (n (%))	PNH (n (%))
Visit 2 (CIP, n = 119; PNH, n = 113)		
Eradication	3 (3)	—
Presumed eradication	90 (76)	86 (76)
Persistence	1 (1)	7 (6)
Indeterminate	20 (17)	18 (16)
Superinfection	5 (4)	2 (2)
Visit 3* (CIP, n = 107; PNH, n = 98)		
Eradication/presumed eradication	84 (78)	76 (78)
Indeterminate	23 (21)	19 (19)
Reinfection	1 (1)	2 (2)
Recurrence	—	1 (1)

\*Only for cured patients at visit 2.

*Streptococcus pneumoniae*, other *Enterobacteriaceae*, other pathogens). Superinfection was identified in 7 patients, 5 in the CIP group (*S epidermidis* [2], *P mirabilis*, *Candida* sp, other pathogens) and 2 in the PNH group (*Candida* sp, *Streptococcus* sp).

At visit 3, eradication (including presumed eradication) was maintained at a rate of 78% in both treatment groups. In 42 patients no culture was done, and these infections were classified as indeterminate. Three reinfections, 1 in the CIP group (*S aureus*) and 2 in the PNH group (*P aeruginosa*, *Pseudomonas* sp), and 1 recurrence in the PNH group (*P aeruginosa*) were seen at the 1-month follow-up visit at the end of treatment.

### Safety

The safety analysis was carried out in the population of randomized patients who received at least 1 dose of the study treatment (N = 318). Adverse events were recorded in 24 (15%) patients in the CIP group and 12 (8%) patients in the PNH group. The number of patients with adverse reactions to the drugs (possibly, probably, or very probably associated) dropped to 15 (9%) in the CIP group and 7 (5%) in the PNH group.

Among the 25 drug-related adverse events reported in 22 patients, the most frequent were pruritus (4 CIP, 2 PNH), stinging (3 CIP, 2 PNH), earache (2 CIP, 3 PNH), passage of the medication into the mouth (2 CIP, 1 PNH), vertigo (2 CIP), and cephalgia (2 CIP). Eight subjects withdrew from the study because of an adverse event that was not considered to be related to the drug in the 4 CIP cases or related to PNH in 2 of 4 cases.

Pretreatment and posttreatment audiometric tests were available in 295 patients (157 in the CIP group, 138 in the PNH group). No changes in the audiometric assessment were recorded in the CIP group. One patient in the PNH group evolved from a normal audiogram at visit 1 to hearing loss at all frequencies at visit 3.

No plasma levels of ciprofloxacin were detected among the 14 subjects (9 CIP, 5 PNH) from whom blood was drawn 1 to 2 hours after the first dosing.

## DISCUSSION

Designed as a therapeutic equivalence study, this trial required the primary efficacy variable to be analyzed on a large number of patients who satisfied all protocol requirements (per protocol population) and were randomly allocated to either study treatment. We managed to rely on 232 comparable and fully compliant subjects. On the basis of the observed clinical cure rates, we calculated the power of the study a posteriori. According to the formulas of Machin and Campbell,<sup>17</sup> the study had a power greater than 95% to conclude the therapeutic equivalence between the two treatments.

Because it was impossible to carry out the trial under double-blind conditions, we tried to avoid any subjective assessment of the investigator by selecting a primary efficacy end point (clinical cure) based on objective observations, such as disappearance of otorrhea or presence of serous/mucous discharge giving negative cultures.

Both treatments showed a high degree of success based on both clinical and bacteriologic responses.

The difference observed between the two treatments in clinical cure rates (-4%) showed a confidence interval ranging from -8.86% to 4.48%, an interval that is entirely below the maximum value (15%), which was defined as therapeutic equivalence in the study protocol. Similarly, the data obtained in the evaluable patients and the randomized patients did not show any inferiority of ciprofloxacin and rather pointed toward a higher cure rate under ciprofloxacin because the confidence intervals showed negative values on both sides.

The clinical cure (91%) and bacteriologic eradication (89%) rates seen in the ciprofloxacin-treated patients are higher than those observed after oral administration of ciprofloxacin.<sup>5-7</sup> These 3 studies, carried out in adult patients with CSOM treated with oral ciprofloxacin, 500 mg twice daily, showed that, at the end of the treatment, otorrhea had disappeared in 67%,<sup>5</sup> 59%,<sup>6</sup> or 58%<sup>7</sup> and that bacterial eradication was seen in 59%, 62%, and 70%, respectively. When 750 mg of oral ciprofloxacin<sup>6</sup> was given twice daily, success rates of 70% and 74% were reached as far as otorrhea disappearance and bacteriologic eradication, respectively, were concerned.

Although carried out with slightly different designs and treatment response assessments, similar efficacy results to those observed in the present clinical trial have been reported after topical treatment with different ciprofloxacin concentrations (0.2%, 0.3%, and 0.5%).<sup>8,9,12-14</sup> In a subset of patients with CSOM,<sup>8</sup> cure rates were seen in 80% and 71% of the patients treated

with 0.5% or 0.2% ciprofloxacin solutions. As compared with oral treatment (500 mg twice daily), topical treatment<sup>9</sup> with 0.2% ciprofloxacin solution resulted in significantly higher percentages of clinical improvement or cure (95% vs 68%) and microbiologic eradication (95% vs 55%); furthermore, combining oral and topical therapy did not further enhance the efficacy (90% clinical improvement or cure). In a study<sup>12</sup> comparing otic applications of ciprofloxacin 0.3% solution and gentamicin 0.3% solution, clinical cure (absence of otorrhea) was found in 95% and 94%, and bacteriologic eradication in 96% and 93% of the patients, respectively.

A recently published meta-analysis of 24 clinical trials involving 1660 patients reviewed the effectiveness of different medical treatments of CSOM.<sup>18</sup> Topical treatment with antibiotics or antiseptics was more effective than treatment with systemic antibiotics in resolving otorrhea and in eradicating bacteria. Combining topical and systemic antibiotics was no more effective than using topical antibiotics alone. Regarding topical antibiotic treatments, quinolones were more effective than nonquinolones.

Topical treatments are highly desirable in children, considering the high incidence of CSOM in childhood, mainly as a complication of tympanostomy tube insertion. No oral antibiotics effective against *P aeruginosa* are available for use in children. The potential for ototoxicity of aminoglycoside or antibiotic-steroid otic drops has limited their use in children. Ototoxicity has been investigated as a possible adverse effect of ototopical ciprofloxacin therapy in several animal<sup>3,10,11</sup> and clinical<sup>5-9,12-14</sup> studies. No study has documented ototoxicity of ciprofloxacin after topical application of 1.55 to 7.5 mg/mL solutions.

Two studies<sup>13,14</sup> in children aged 1 to 14 years with otorrhea due to *P aeruginosa* indicate that ciprofloxacin, 3 drops of a 0.3% solution applied topically 3 times daily for 14 days, resulted in clinical cure rates of 91% and 69%. Bone-conduction audiometry tests performed at baseline and at the end of treatment showed no relevant changes in hearing.<sup>13</sup>

The distribution of causal agents, similar within our two treatment groups, showed that *Staphylococcus*, *P aeruginosa*, and other gram-negative bacilli were the most prevalent micro-organisms, although a higher incidence of *Pseudomonas* over *Staphylococcus* is usually described.<sup>2</sup>

In the CIP group, 84% of the causal pathogens isolated were sensitive to ciprofloxacin, whereas those isolated in the PNH group were sensitive to polymyxin B and/or neomycin in 76% of the cases; this difference may explain the slightly better results obtained with ciprofloxacin in our primary efficacy end point and indicates to what extent the use of ciprofloxacin adjusts to our environmental conditions.

Both treatments were equally well tolerated, with a higher incidence of adverse drug events in the CIP group (9%) as compared with the PNH group (5%). Because most adverse events were of local nature, the predominant incidence observed with ciprofloxacin might be attributed to the greater volume instilled into the ear with each application (0.50 mL CIP vs 0.15 mL PNH). In no case was the treatment with ciprofloxacin interrupted after an adverse drug reaction, and no articular complaint was recorded.

Audiometric assessment did not find any changes in hearing by 1 month after the end of ciprofloxacin treatment, as previously reported in other studies.<sup>12,13,19,20</sup> Ciprofloxacin was not detected in the plasma samples of the 14 patients who were tested with an analytical sensitivity of 10 µg/L, suggesting that the compound is not absorbed into the systemic circulation<sup>13</sup> when administered topically in a 0.2% solution to patients with tympanic membrane perforation.

On the basis of clinical and bacteriologic data, we can conclude that a 0.2% otic solution of ciprofloxacin supplied in single-dose containers is at least as effective as an otic suspension combining polymyxin B, neomycin, and hydrocortisone (Otosporin) in neutralizing the recurrent exacerbation of CSOM.

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## REFERENCES

1. Jahn AF. Chronic otitis media: diagnosis and treatment. *Med Clin North Am* 1991;75:1277-91.
2. Wintermeyer SM, Nahata MC. Chronic suppurative otitis media. *Ann Pharmacother* 1994;28:1089-99.
3. Brownlee RE, Hulka GF, Prazma J, et al. Ciprofloxacin. Use as a topical otic preparation. *Arch Otolaryngol Head Neck Surg* 1992;118:392-6.
4. Lundy LB, Graham MD. Ototoxicity and ototopical medications: a survey of otolaryngologists. *Am J Otol* 1993;14:141-6.
5. Gehanno P, the French Study Group. Multicenter study of the efficacy and safety of oral ciprofloxacin in the treatment of chronic suppurative otitis media in adults. *Otolaryngol Head Neck Surg* 1997;117:83-90.
6. Fombour JP, Barrault S, Koubbi G, et al. Study on the efficacy and safety of ciprofloxacin in the treatment of chronic otitis. *Chemotherapy* 1994;40(Suppl 1):29-34.
7. Legent F, Bordure Ph, Beauvillain B, et al. Controlled prospective study of oral ciprofloxacin versus amoxicillin/clavulanic acid in chronic suppurative otitis media in adults. *Chemotherapy* 1994;40(Suppl 1):16-23.
8. García-Rodríguez JA, Del Cañizo A, García Sánchez JE, et al. Efficacy of 2 regimens of local ciprofloxacin in the treatment of ear infections. *Drugs* 1993;45(Suppl 3):327-8.
9. García Rodríguez JA, García Sánchez JE, García García MI, et al. Efficacy of topical ciprofloxacin in the treatment of ear infections in adults. *J Antimicrob Chemother* 1993;31:452-3.
10. Claes J, Govaerts PJ, Van de Heyning PH, et al. Lack of ciprofloxacin ototoxicity after repeated ototopical application. *Antimicrob Agents Chemother* 1991;35:1014-6.
11. Lutz H, Lenarz T, Gotz R. Ototoxicity of gyrase antagonist ciprofloxacin? *Adv Otorhinolaryngol* 1990;45:175-80.
12. Lorente J, Sabater F, Maristany M, et al. Estudio multicéntrico comparativo de la eficacia y tolerancia de ciprofloxacino tópico (0,3%) versus gentamicina tópica (0,3%) en el tratamiento de la otitis media crónica simple no colesteatomatosa en fase supurativa. *Ann Iber-Amer* 1995;XXII:521-33.
13. Force RW, Hart MC, Plummer SA, et al. Topical ciprofloxacin for otorrhea after tympanostomy tube placement. *Arch Otolaryngol Head Neck Surg* 1995;121:880-4.
14. Wintermeyer SM, Hart MC, Nahata MC. Efficacy of ototopical ciprofloxacin in pediatric patients with otorrhea. *Otolaryngol Head Neck Surg* 1997;116:450-3.
15. Ear preparations (1997:0652). In: European Pharmacopoeia Commission. *European Pharmacopoeia*. 3rd ed. Strasbourg: Council of Europe; 1997.
16. Committee for Proprietary Medicinal Products. Note for guidance on evaluation of new anti-bacterial medicinal products. CPMP/EWP/558/95. April 1997.
17. Machin D, Campbell MJ. *Statistical tables for the design of clinical trials*. Oxford: Blackwell Scientific Publications; 1987.
18. Acuin J, Smith A, Mackenzie I. Treatment of chronic suppurative otitis media (Cochrane review). In: *The Cochrane Library*. Issue 1. Oxford: Update Software; 1999.
19. Ganz H. Bakterielle Otitis externa mit Überschreitung der Organengrenzen—systemische und lokale Kombinationsbehandlung mit Ciprofloxacin. *Z Artzl Fortbild* 1993;87:413-5.
20. De Schepper S, Schmelzer B. Lokale behandeling van otitis media en otitis externa: rol van de quinolones. *Acta Otorhinolaryngol Belg* 1994;48:67-70.

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