Comparison of two otologic suspensions of ciprofloxacin 2 mg/mL and hydrocortisone 10 mg/mL in the treatment of otitis externa: a multicenter, double-blind, randomized study

Comparação de duas suspensões otológicas de ciprofloxacino 2 mg/mL e hidrocortisona 10 mg/mL no tratamento da otite externa: um estudo multicêntrico, duplo-cego e randomizado

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RBM Maio 15 V 72 N 5
págs.: 189-194

Indexado LILACS LLXP: S0034-72642015017800002

Unitermos: acute diffuse otitis externa, ciprofloxacin 2 mg/mL, hydrocortisone 10 mg/mL, otologic suspension.
Unterms: otite externa aguda difusa, ciprofloxacino 2 mg/mL, hidrocortisona 10 mg/mL, suspensão otológica.

Sumário
This was Phase III multicenter, double-blind, randomized, comparative safety and efficacy study in parallel groups of subjects, assessing non-inferiority between two commercially available otologic suspensions containing ciprofloxacin 2mg/mL and hydrocortisone 10mg/mL (Otociriax and Cipro HC®) in the treatment of acute diffuse otitis externa. Following screening and informed consent, subjects were randomly allocated into two treatment groups: Group A (treated with Otociriax) and Group B (treated with Cipro HC®). Treatment regimen in both groups was three drops, twice daily for seven days. The primary study endpoint was otitis cure, defined as elimination of pain, edema, and otorrhea. The secondary study endpoint was presence of side effects. Efficacy assessments included presence and intensity of otitis externa manifestations. Safety assessments included vital signs and physical examination, as well as adverse event monitoring. Study data analysis was performed using GraphPad Prism 5.0. For categorical variables, we used the c2 or Fisher's test, while continuous variables were analyzed using the ANOVA or Student's T test. A total of 265 subjects were randomized to treatment, with 132 subjects in Group A and 133 in Group B. There were no statistically significant pretreatment differences between the two treatment groups (p>0.05 for all variables). All subjects presented manifestations of acute diffuse otitis externa at pretreatment. There were statistically significant improvements (p<0.05) in each parameter of otitis externa assessed in both treatment groups. At the end of the treatment period, 96 (82.05%) subjects in Group A and 100 subjects (86.97%) in Group B were completely symptom-free, with no statistically significant difference between treatment groups in symptom remission (c2=2.147; df=3; p=0.542). Overall, no unfavorable alteration was detected in the safety parameters monitored, in either treatment group. Adverse events were reported among 11 subjects in Group A and 7 subjects in Group B. There was no statistically significant between-group difference in incidence (p=0.463), duration (c2=13.55; df=7; p=0.06), or distribution of causality assessment (p=0.4) of the adverse events. The results of this study clearly indicate that there was no difference in treatment results between the two patient groups. Both treatments were safe and effective in treating the signs and symptoms of otitis externa as evidenced by the assessments performed throughout the treatment period. Treatment with Otociriax was non-inferior to treatment with Cipro HC® in the patient population evaluated in this study.

Summary
Este foi um estudo Fase III multicêntrico, duplo-cego, randomizado e comparativo de segurança e eficácia em grupos paralelos de pacientes, avaliando a não-inferioridade entre duas suspensões otológicos disponíveis comercialmente contendo ciprofloxacina 2 mg/ml e hidrocortisona 10 mg/mL (Otociriax e Cipro HC®), no tratamento da otite externa aguda difusa. Após a triagem e consentimento informado, os indivíduos foram alocados aleatoriamente entre dois grupos de tratamento: Grupo A (tratado com

Otociriax) e Grupo B (tratado com Cipro HC®). O regime de tratamento em ambos os grupos foi de três gotas, duas vezes por dia durante sete dias. O desfecho primário do estudo foi a cura da otite, definida como eliminação da dor, edema, e otorreia. O desfecho secundário foi a presença de efeitos colaterais. A avaliação de eficácia incluiu a presença e intensidade das manifestações de otite externa. As avaliações de segurança incluíram sinais vitais e exame físico, bem como o monitoramento de eventos adversos. A análise dos dados do estudo foi realizada utilizando GraphPad Prism 5.0. Para as variáveis categóricas, foi utilizado o teste c2 ou teste de Fisher, enquanto as variáveis contínuas foram analisadas usando o ANOVA ou teste T de Student. Um total de 265 indivíduos foram randomizados para o tratamento, com 132 indivíduos no grupo A e 133 no Grupo B. Não houve diferenças pré-tratamento estatisticamente significativas entre os dois grupos de tratamento (p>0,05 para todas as variáveis). Todos os sujeitos apresentaram manifestações da otite externa aguda difusa no pré-tratamento. Houve melhora estatisticamente significativa (p<0,05) em cada parâmetro de otite externa avaliada em ambos os grupos de tratamento. No final do período de tratamento, 96 (82,05%) indivíduos do grupo A e 100 indivíduos (86,97%) no grupo B estavam completamente livre de sintomas, não havendo diferença estatisticamente significativa entre os grupos de tratamento na remissão dos sintomas (c2=2,147; df=3; p=0,542). Em geral, nenhuma alteração desfavorável foi detectada nos parâmetros de segurança monitorados, em cada grupo de tratamento. Eventos adversos foram relatados entre 11 indivíduos do grupo A e 7 indivíduos do Grupo B. Não houve diferença estatisticamente significativa entre os grupos na incidência (p=0,463), duração (c2=13,55; df=7; p=0,06), ou distribuição de avaliação de causalidade (p=0,4) dos eventos adversos. Os resultados deste estudo indicam claramente que não houve diferença nos resultados do tratamento entre os dois grupos de pacientes. Ambos os tratamentos foram seguros e eficazes no tratamento dos sinais e sintomas da otite externa como evidenciado pelas avaliações realizadas durante todo o período de tratamento. O tratamento com Otociriax não foi inferior ao tratamento com Cipro HC® na população de pacientes avaliados neste estudo.

Abstract

This was Phase III multicenter, double-blind, randomized, comparative safety and efficacy study in parallel groups of subjects, assessing non-inferiority between two commercially available otologic suspensions containing ciprofloxacin 2mg/mL and hydrocortisone 10mg/mL (Otociriax and Cipro HC®) in the treatment of acute diffuse otitis externa. Following screening and informed consent, subjects were randomly allocated into two treatment groups: Group A (treated with Otociriax) and Group B (treated with Cipro HC®). Treatment regimen in both groups was three drops, twice daily for seven days. The primary study endpoint was otitis cure, defined as elimination of pain, edema, and otorrhea. The secondary study endpoint was presence of side effects. Efficacy assessments included presence and intensity of otitis externa manifestations. Safety assessments included vital signs and physical examination, as well as adverse event monitoring. Study data analysis was performed using GraphPad Prism 5.0. For categorical variables, we used the c2 or Fisher's test, while continuous variables were analyzed using the ANOVA or Student's T test. A total of 265 subjects were randomized to treatment, with 132 subjects in Group A and 133 in Group B. There were no statistically significant pretreatment differences between the two treatment groups (p>0.05 for all variables). All subjects presented manifestations of acute diffuse otitis externa at pretreatment. There were statistically significant improvements (p<0.05) in each parameter of otitis externa assessed in both treatment groups. At the end of the treatment period, 96 (82.05%) subjects in Group A and 100 subjects (86.97%) in Group B were completely symptom-free, with no statistically significant difference between treatment groups in symptom remission (c2=2.147; df=3; p=0.542). Overall, no unfavorable alteration was detected in the safety parameters monitored, in either treatment group. Adverse events were reported among 11 subjects in Group A and 7 subjects in Group B. There was no statistically significant between-group difference in incidence (p=0.463), duration (c2=13.55; df=7; p=0.06), or distribution of causality assessment (p=0.4) of the adverse events. The results of this study clearly indicate that there was no difference in treatment results between the two patient groups. Both treatments were safe and effective in treating the signs and symptoms of otitis externa as evidenced by the assessments performed throughout the treatment period. Treatment with Otociriax was non-inferior to treatment with Cipro HC® in the patient population evaluated in this study.

Introduction

The ear is divided into three parts: external, middle, and inner ear. The external ear is formed by the pinna and external auditory meatus, at the end of this canal is the tympanic membrane. Behind the tympanic membrane lie the middle and inner ear. Otitis externa (OE) is a type of infection affecting the external auditory canal. The warm, humid, dark environment of the ear canal provides favorable conditions for inflammation and/or infection by bacterial or fungal species1.

Acute diffuse otitis externa is a very common condition in tropical countries, responsible for a large number of otorhinolaryngology emergency room visits, particularly in the summer5. It is characterized by acute and diffuse inflammation of the skin covering and the subcutaneous tissue of the outer ear. The predominant cause of OE is bacterial and the principal manifestation is otalgia, the intensity of which may vary from mild to severe. Small quantities of mucopurulent otorrhea may also be observed, in addition to auricular fullness, hypoacusia, and pruritus9. Physical examination often reveals hyperemia of the external ear canal, with small quantities of mucopurulent discharge. In some case, the tympanic membrane may not be visible due to the intense edema of the ear canal, while in other cases thickness and hyperemia of the tympanic membrane is noted, which may give a false impression of otitis media. Painful retro and preauricular adenomegaly may also be found, in addition to edema of the tissues surrounding the ear1,8.

Factors contributing to the pathophysiology of otitis externa include obstruction, absence of cerumen, trauma, and alteration of the pH of the ear canal. Inflammation and skin edema lead to obstruction of adjacent structures and pruritus, which in turn favor alterations in the quality and quantity of cerumen, epithelial migration, and changes in pH of the ear canal. As previously mentioned, the dark, alcaline, ear canal provides a favorable breeding ground for microorganisms 10.

Excessive cleaning of the ear and/or scratching of the ear canal not only removes cerumen but also creates abrasions in the thin layer of skin of the ear canal, allowing access of microorganisms to deeper tissue. Swimming is also an important risk factor for the development of otitis externa 10.

Approximately 38% of otitis externa infections are by P. aeruginosa, with staphylococcal infections corresponding to approximately 25% of isolated organisms, among which S. epidermidis and S.aureus are the most common. The second largest group of gram-positive bacteria belong to the diphtheroid family, and includes M. otitidis and M. alconae. Enterobacteriaceae and Vibronaceae species correspond to approximately 8.5% of identified etiologic agents. In decreasing order of frequency are: Enterobacter, Klebsiella, Serratia, Proteus, and E. coli 7.

The clinical picture of otits externa includes intense, radiating pain to the temporal and mandibular regions, sensitivity to palpation and manipulation of the ear, loss of conductive audition and ear swelling by edema, together with external ear canal stenosis due to accumulation of debris and secretions. Upon physical examination, the canal is erythematous and presents inflammatory infiltration that may progress to stenosis and the presence of phlegmonosum accumulation. Purulent otorrhea, vesicles, false membranes and crusted lesions may also be observed. In more advanced cases, fever and pre- and postauricular anterior cervical lymphadenopathy may also be present 1,9.

Acute otitis externa can be divided into two stages, pre-inflammatory and inflammatory. The pre-inflammatory stage is associated with mild pain, edema and swelling of the external ear, while the inflammatory stage can be subcategorized into mild, moderate, and severe. In the mild inflammatory stage, pruritus, progressive pain, and discrete edema is observed; the outer ear canal is unobstructed. In the moderate stage, increased pain and edema are noted and the outer ear canal is partially obstructed by edema and secretion. The severe stage is associated with severe pain that worsens with mastigation and dislocation of the skin surrounding the ear. The lumen of the outer ear canal is obliterated by secretion, increased edema and erythema, usually with signs of dissemination to surrounding tissues and regional lymph nodes 9.

Acute diffuse OE is diagnosed by examination of the ear with an otoscope. During the exam, the following signs and symptoms are noted: swelling or redness of the skin of the outer ear canal; secretion or lesions in the canal; swollen lymph nodes near the ear1.

Treatment of acute diffuse OE combines systemic and topical treatments which aim to address the symptoms presented by the patient. Pain is treated with systemic medications, such as acetaminophen, ibuprofen, codein, and diclofenac. Topical treatment with antibiotic ear drops is indicated in cases of localized infection in the external ear canal, without extension to neighboring areas. Systemic antibiotic use is not recommended for uncomplicated cases 2,3,4,6,10.

In this study, we evaluated the use of two topical formulations combining antibiotic (ciprofloxacin) with a steroid (hydrocortisone) in the treatment of acute diffuse otitis externa.

Material & Methods

This was a Phase III multicenter, double-blind, randomized, comparative safety and efficacy study in parallel groups of subjects, assessing non-inferiority between two commercially available otologic suspensions containing ciprofloxacin 2 mg/mL and hydrocortisone 10 mg/mL (Otociriax and Cipro HC®). The study protocol was submitted to and approved by the ethical committee of each participating institution.

Following screening and informed consent, subjects of both genders between the ages of 1 and 70 years of age, with a clinical diagnosis of acute otitis externa, were randomized into two treatment groups: Group A was treated with Otociriax; while subjects in group B were treated with Cipro HC®. Treatment regimen in both groups was three drops, twice daily for seven days. Randomization lists were generated for each study center.

Safety and efficacy assessments were carried out throughout the treatment period. Two study visits were conducted: Pretreatment and Post-treatment. Pretreatment procedures included clinical assessment, verification of inclusion and exclusion criteria, signature of the informed consent form and subject inclusion; subjects also received a diary containing questions to be answered during the treatment period, returned at the end of the study. At treatment day 3 and treatment day 6, a member of the clinical study team telephoned the patient to inquire about treatment compliance, occurrence of adverse events, and symptom severity. The Post-treatment visit took place between the 8th and 11th day following treatment initiation. Subjects returned to the study center for clinical assessments of safety and efficacy and returned study medication and diaries. Use of concomitant medications was monitored throughout the study period.

The primary study endpoint was otitis cure, defined as elimination of pain, edema, and otorrhea. The secondary study endpoint was identification of side effects caused by use of the study medication. Efficacy assessments included presence and intensity (mild, moderate, or severe) of otitis externa manifestations: dermal inflammation, otalgia, pain on compression, otorrhea, hypoacusia, pruritus, hyperemia of the ear canal, edema of the ear canal, adenomegalia, edema of surrounding tissues, and fever. Safety assessments included vital signs and physical examination, as well as adverse event monitoring (occurrence, severity, duration, resolution, and relation to study drug).

Data from each center were tabulated, merged in a single database, and unblinded after the end of the study treatment period. Results were statistically analyzed using the software GraphPad Prism 5.0. Overall clinical efficacy and tolerability were analyzed via comparison of the results of each assessment in relation to pretreatment values, within and between treatment groups. For categorical variables, we used the c2 or Fisher's test, while continuous variables were analyzed using the ANOVA or Student's T test.

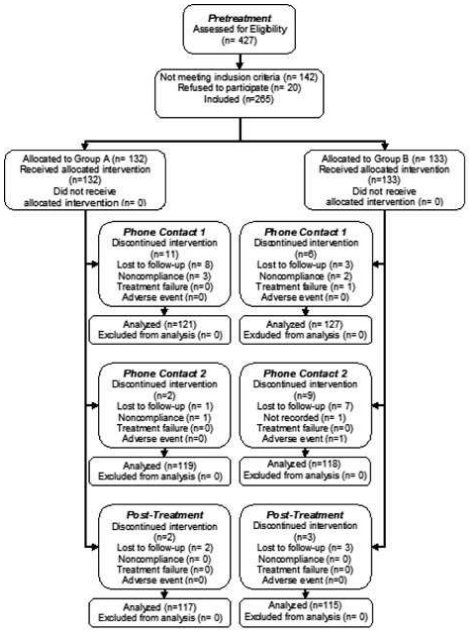

Figure 1. Flowchart of subjects through the study.

Results

A total of 265 subjects were randomized to treatment, with 132 subjects in Group A and 133 in Group B. Figure 1 shows the flow of subjects throughout the study. There were no statistically significant pretreatment differences between the two treatment groups in distribution of gender, age, physical exam results, weight, vital signs, temperature, and otitis manifestations ($p>0.05$ for all variables). Table 1 summarizes the demographic and pretreatment characteristics of the study population.

All subjects presented manifestations of acute diffuse otitis externa at pretreatment. The assessments of otitis of each patient group at Pre- and Post-Treatment are summarized in Table 2. There were statistically significant improvements ($p<0.05$) in each parameter assessed in both treatment groups.

There were no statistically significant between-group differences during the first and second telephone contacts which took place at treatment day 3 and treatment day 6 ($p>0.05$ for all assessments). At Telephone Contact 1, symptoms were absent among 22 subjects in Group A and 27 subjects in Group B. The distribution of subject-reported symptom intensity during Telephone Contact 1 was reported as "Minimal" among 51/50 subjects in treatment groups A and B, respectively, "Moderate" among 41/46 subjects, and "Intense" among 4/3 subjects in treatment groups A and B, respectively. At Telephone Contact 2, 75 subjects in Group A and 68 subjects in Group B reported absence of symptoms. The distribution of subject-reported symptom intensity was reported as "Minimal" among 37/38 subjects in treatment groups A and B, respectively, "Moderate" among 6/11 subjects, and "Intense" among 1/0 subjects in treatment groups A and B, respectively.

Table 1. Demographic data and pretreatment characteristics

Demographic data: findings on admission	Group A	Group B
Gender (n)		
Female	76	65
Male	56	68
Ethnicity		
Asian	3	2
Black	26	21
Caucasian	50	67
Mulatto	53	42
Age (years)	38.92 (±12.03)	37.72 (±12.2)
Weight (kg)	71.79 (±11.74)	71.76 (±12.38)
Blood pressure (mmHg)		
Systolic	120.9 (±7.25)	121.1 (±7.49)
Diastolic	77.01 (±9.37)	76.01 (±9.57)
Heart rate (bpm)	69.25 (±8.20)	69.88 (±7.86)
Respiratory rate (ipm)	15.36 (±2.22)	15.37 (±2.25)
Temperature (°C)	35.69 (±0.89)	35.92 (±0.73)

Data are n *or means (±SD).*

Table 2. Manifestations of acute diffuse otitis externa at pre- and post-treatment

OE manifestation	Group A		Group B	
	Pre-treatment	Post-treatment	Pre-treatment	Post-Treatment
Dermal inflammation	111	1	113	5
Otalgia	130	5	125	2
Pain on compression	113	2	118	2
Otorrhea	42	0	45	0
Hypoacusia	68	0	71	5
Pruritus	107	10	107	3
Hyperemia of the ear canal	126	6	126	5
Edema of the ear canal	117	0	119	0
Adenomegaly	23	0	25	0
Edema of surrounding tissues	18	4	28	3
Fever	2	0	6	0
Other symptoms	13	0	11	0

Data are n.

Table 3. Safety Evaluations

	Group A			Group B			
	Pre-treatment	Post-treatment	Change from pre-treatment	Pre-treatment	Post-treatment	Change from pre-treatment	Between-group difference
Weight (kg)	71.79 (±11.74)	71.62 (±11.9)	no (p=0.062)	71.76 (±12.38)	71.55 (±12.77)	no (p=0.517)	no (p=0.967)
Systolic BP (mmHg)	120.9 (±7.25)	120.6 (±7.73)	no (p=0.671)	121.1 (±7.49)	120.2 (±7.702)	yes (p=0.011)	no (p=0.771)
Diastolic BP (mmHg)	77.01 (±9.37)	75.69 (±9.18)	no (p=0.07)	76.01 (±9.57)	75.74 (±10.24)	no (p=0.953)	no (p=0.969)
Heart rate (bpm)	69.25 (±8.20)	69.49 (±6.65)	no (p=0.793)	69.88 (±7.86)	68.53 (±7.23)	no (p=0.223)	no (p=0.327)
Respiratory rate (ipm)	15.36 (±2.22)	15.34 (±2.24)	no (p=0.503)	15.37 (±2.25)	15.17 (±1.98)	no (p=0.229)	no (p=0.327)
Temperature (°C)	35.69 (±0.89)	35.6 (±0.84)	yes (p=0.034)	35.92 (±0.73)	35.72 (±0.66)	yes (p=0.002)	no (p=0.267)

At the end of the treatment period, 96 (82.05%) subjects in Group A and 100 subjects (86.97%) in Group B were completely symptom-free, with no statistically significant difference between treatment groups in symptom remission (c2=2.147; df=3; p=0.542) (Figure 2).

The results of the safety evaluations performed during the study are summarized in Table 3. Overall, no unfavorable alteration was detected in the safety parameters monitored, in either treatment group. Adverse events were reported among subjects in both treatment groups, with 11 subjects in Group A and 7 subjects in Group B reporting occurrence of adverse events. The adverse events recorded during the treatment period are summarized in Table 4. There was no stainitiated prior to obtaining culture results in most instances, given that treatment is geared toward the most commonly identified bacterial pathogens found among patients with otitis externa10,11. Topical treatment provides the advantage of delivering a higher drug dosage directly to the site of infection independently of systemic administration, resulting in a more favorable safety profile with a lower risk of adverse effects. The addition of hydrocortisone to the antibiotic in an ear drop formulation offers the potential for significant reduction of treatment time to pain relief 12.

The results of this study clearly indicate that there was no difference in treatment results between the two patient groups. Both treatments were equally safe and effective in treating the signs and symptoms of otitis externa as evidenced by the assessments performed throughout the treatment period. Treatment with Otociriax was non-inferior to treatment with Cipro HC® in the patient population evaluated in this study.

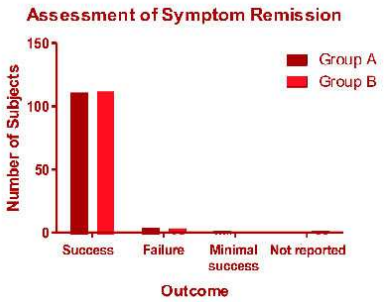

Figure 2. Assessment of symptom remission

Table 4. Adverse events

Adverse event	Number of subjects affected
Amigdalitis	1
Auricular pruritus	2
Cough	1
Dizzinnes	1
Dysphagia	1
Eczema and pruritus adjacent to left ear	1
Hair loss	1
Headache	1
Headache	4
Headache	1
Headache with radiating trigeminal pain	1
Left side hypoacusia	1
Numbness	1
Obstruction of the other ear	1
Pain radiating to the jaw	1
Pruritus	4
Tingling	1

Data are n

Acknowledgements

The authors would like to thank the following individuals for their contributions to this study: Silvia Maciel, Dra. Anna Milena Fraga, Dra. Bárbara Elvina Queiroz, Dra. Mirella Metidieri, Lisa Oliveira, Dr. Thiago Cavalcante Ribeiro, Dr. Gustavo Barreto da Cunha, Aline P. M. da Silva, Dr. Gustavo Lino Nóbrega da Silva, Dra. Tatiane Costa Camurugy, Dr. Ramirez Ribeiro Fidelis, Izilda Fátima Daloia, Daiane Bergamim, and Mario Nilo.

Bibliografia

1. Bailey BJ, Baroody FM, Dohar JE, Guthrie RM, Harris JS, Roland PS, Shulman ST, Weis MS, Whitsell DL. Diagnosis and Treatment of Acute Otitis Externa an Interdisciplinary Update. Ann of Otol. Rhino, & Laryn, Feb 1999 (Supp 176); 108(2):2.
2. Center for drug evaluation and research. Food and Drug Administration.
3. Dohar JE. Evolution of management approaches for otitis externa. Pediatr Infect Dis J. 2003 Apr;22(4):299-305.
4. Dohar JE. Update on AOM, EO and Chronic OM. Seminars in OM management. BC Decker INC. 1998.
5. Figueirede RR, Fabri ML, Machado WS. Acute diffuse external otitis: a prospective study in Rio de Janeiro summer. Rev. Bras. Otorrinolaringol. 2004 mar, 70 (2): 226 - 31.
6. H.P. Hang, M.M. Dale, I.M. Ritter, O.K. Noore. Farmacologia 5ª edição, 2004: 736 - 737.
7. Nogueira JCR, Diniz MFM, Lima EO, Lima ZN. Identification and antimicrobial susceptibility of acute external otitis microorganisms. Revista Brasileira de Otorrinolaringologia, 2008; 74(4): 526-530.
8. Robins & Cotran. Patologia: Bases Patológicas das doenças 7ª edição, 2005: 828.
9. Rosenfeld RM, Schwartz SR, Cannon CR, et al. Clinical Practice Guideline Acute Otitis Externa. Otolaryngol Head and Neck Surg, 2014 Feb; 150(1 Suppl):S1-S24.
10. Sander R. Otitis externa: a practical guide to treatment and prevention. Am Fam Physician. 2001 Mar 1;63(5):927-36, 941-2.
11. Sclar DA, Tartaglione TA, Fine MJ. Overview of issues related to medical compliance with implications for the outpatient management of infectious diseases. Infect Agents Dis. 1994 Oct; 3(5):266-73.
12. Wintermeye SM, Hart MC, Nahata MC. Efficacy of ototopical ciprofloxacin in pediatric patients with otorrhea. Otolaryngol Head Neck Surg. 1997 Apr; 116(4):450-3.