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Study No.: 541
Title: The Effect of Antimicrobial Therapy for Otitis Media on Nasopharyngeal Pneumococcal Carriage and Antibiotic Resistance.
Rationale: The incidence of pneumococcal resistance to antimicrobials is increasing globally but little is known regarding the relative effects of the use of different oral antimicrobials on carriage of resistant organisms. This study compared the changes in the prevalence and resistance profiles of strains of <i>S. pneumoniae</i> , <i>H. influenzae</i> , viridans streptococci, and <i>S. aureus</i> in nasopharyngeal samples from children treated with amoxicillin/clavulanate ES-600 with changes seen after treatment with azithromycin.
Phase: III
Study Period: 16 March 1999 to 19 February 2001.
Study Design: Randomized, open-label, comparative study.
Centers: Single center (United States).
Indication: Acute Otitis Media (AOM)
Treatment: Subjects randomized to amoxicillin/clavulanate ES-600 received doses of 90/6.4 mg/kg a day in two equal doses given every 12 hours immediately prior to food (i.e., breakfast and dinner). Subjects randomized to azithromycin received 10 mg/kg on Day 1 and 5 mg/kg on Days 2-5, given once daily on an empty stomach, (i.e., either 1 hour before or at least 2 hours after a meal). The volume of the dose for the subject's weight range was listed in a Recommended Dosing Chart provided by the sponsor. Subjects were instructed to attend the clinic at three visits: Diagnosis/Screening (Visit 1, Day 1), End of Therapy (Visit 2, Day 12-14), and Follow Up (Visit 3, Day 58-62)
Objectives: The primary objective was to assess the prevalence of nasopharyngeal carriage of <i>S. pneumoniae</i> and the percentage of drug-resistant strains of <i>S. pneumoniae</i> isolated from children treated for acute otitis media (AOM).
Primary Outcome/Efficacy Variable: Two primary variables were used in this study: the prevalence of nasopharyngeal carriage of <i>S. pneumoniae</i> before and after therapy for AOM; and the percentage of drug-resistant pneumococcal strains arising after the use of antimicrobials.
Secondary Outcome/Efficacy Variable(s): The rates of nasopharyngeal carriage of other common bacteria (<i>H. influenzae</i> , viridans streptococci, <i>S. aureus</i>). The changes in rates of nasopharyngeal carriage of these pathogens in each treatment group 2 weeks and 2 months after diagnosis of AOM, compared with baseline values. The specific serotypes of <i>S. pneumoniae</i> strains isolated at various times during the study. The rate of nasopharyngeal carriage of methicillin-resistant <i>S. aureus</i> . Clinical outcome (success or failure) at the End of Therapy visit (Day 12-16). Clinical success was defined as sufficient resolution of specific symptoms of AOM and otoscopic signs of acute infection with inflammation, with or without middle ear effusion, such that no additional antibacterial therapy for AOM was indicated. Clinical failure was recorded when there was insufficient improvement of AOM at end of therapy, requiring additional antibacterial therapy prescribed for treatment of AOM. Clinical improvement was defined as improvement, but incomplete resolution of specific symptoms of AOM or otoscopic signs of acute infection with inflammation, with or without middle ear effusion, such that no additional antimicrobial therapy was prescribed for treatment of AOM. Clinical failure at follow-up was defined as the inability to clear or improve the specific symptoms of AOM and otoscopic signs of acute infection with inflammation after three or more days of therapy. If a valid assessment of the clinical outcome could not be made, the subject was counted as a clinical failure.
Statistical Methods: The only subject population analyzed was the Intent-to-Treat (ITT) population, which consisted of all subjects who received at least one dose of study medication. For analysis of bacteriology findings at a particular visit, the ITT population was restricted to those subjects with reported results for that visit. The ITT population was also used as the Safety Population. Summary data were presented as numbers and percentages of subjects in each treatment group, with the exception of age, which was presented using the mean and standard deviation. No formal statistical tests were used in this study.
Study Population: Subjects of either sex, aged 6 months to 6 years, inclusive, and diagnosis of AOM, based on the presence of either purulent otorrhea or at least two of the following symptoms and signs: (a) irritability, (b) acute ear pain, (c) distinct fullness or bulging of the tympanic membrane, and (d) red discoloration of the tympanic membrane. Subjects were not eligible if they had a history of allergy or intolerance to penicillins, cephalosporins or other beta-lactam antimicrobials, or macrolide antimicrobials; had received any systemic antimicrobial in the previous 2 weeks;

were presenting with nausea, vomiting, or water-loss diarrhea; had cleft palate or Down's syndrome; had significant major organ dysfunction, including hepatic or renal impairment; had a history of immune dysfunction or deficiency or were receiving immunosuppressive therapy; had received any investigational drug in the previous 30 days; had phenylketonuria or severe underlying disease (e.g., cardiac disease, cystic fibrosis, neoplasm, diabetes); were currently taking aluminum- or magnesium-containing antacids, theophylline or other methylxanthine medications, probenecid or other tubular secretion inhibitors, or non-sedating antihistamines such as terfenadine and astemizole.		
	Amoxicillin / clavulanate 90/6.4mg/kg/day ES 600	Azithromycin 10mg/kg/day (Day 1) 5mg/kg/day (Day 2-5)
Number of Subjects:		
Planned, N	150 to 200	
Randomized, N	65	69
ITT Population, N	65	69
Completed, n (%)	53 (81.5)	58 (84.0)
Total Number Subjects Withdrawn, n (%)	12 (18.4)	11 (15.9)
Withdrawn due to Adverse Events, n (%)	5 (7.6)	1 (1.4)
Withdrawn due to Lack of Efficacy, n (%)	Not available	Not available
Withdrawn for Other Reasons, n (%)	7 (10.8)	10 (14.5)
Demographics	Amoxicillin / clavulanate 90/6.4mg/kg/day ES 600	Azithromycin
N (ITT)	65	69
Females: Males	30:35	30:39
Mean Age, months (SD)	26.6 (17.9)	23.6 (15.6)
White, n (%)	57 (87.7)	65 (94.2)
Primary Outcome Results: ITT Population		
	Amoxicillin / clavulanate 90/6.4mg/kg/day ES 600	Azithromycin
Prevalence of <i>S. pneumoniae</i> at Each Visit		
Baseline, n/N (%)	33/65 (50.8)	30/69 (43.5)
End of Therapy (Day 12–16), n/N (%)	9/60 (15.0)	20/67 (29.9)
Follow-Up (Day 58-62), n/N (%)	11/57 (19.3)	15/60 (25.0)
Treatment Difference %	Not applicable	
95% CI	Not applicable	
p-value	Not applicable	
Prevalence of Penicillin-Susceptible <i>S. pneumoniae</i> at each visit (minimum inhibitory concentration [MIC] ≥ 0.06 mcg/mL)		
Baseline, n/N (%)	12/65 (18.5)	12/69 (17.4)
End of Therapy (Day 12–16), n/N (%)	2/60 (3.3)	3/67 (4.5)
Follow-Up (Day 58-62), n/N (%)	2/57 (3.5)	3/60 (5.0)
Treatment Difference %	Not applicable	
95% CI	Not applicable	
p-value	Not applicable	
Prevalence of Penicillin-Intermediate <i>S. pneumoniae</i> at Each Visit (minimum inhibitory concentration [MIC] 0.12-1.0mcg/mL)		
Baseline, n/N (%)	10/65 (15.4)	7/69 (10.1)
End of Therapy (Day 12–16), n/N (%)	3/60 (5.0)	11/67 (16.4)
Follow-Up (Day 58-62), n/N (%)	4/57 (7.0)	6/60 (10.0)
Treatment Difference %	Not applicable	
95% CI	Not applicable	
p-value	Not applicable	
Prevalence of Penicillin-Resistant <i>S. pneumoniae</i> at Each Visit (minimum inhibitory concentration [MIC] ≥ 2.0 mcg/mL)		
Baseline, n/N (%)	11/65 (16.9)	11/69 (15.9)
End of Therapy (Day 12–16), n/N (%)	4/60 (6.7)	6/67 (9.0)
Follow-Up (Day 58-62), n/N (%)	5/57 (8.8)	6/60 (10.0)

Treatment Difference %	Not applicable		
95% CI	Not applicable		
p-value	Not applicable		
Prevalence of Azithromycin-Susceptible <i>S. pneumoniae</i> at each visit (minimum inhibitory concentration [MIC] ≤0.5mcg/mL)			
Baseline, n/N (%)	19/65 (29.2)	17/69 (24.6)	
End of Therapy (Day 12–16), n/N (%)	3/60 (5.0)	6/67 (9.0)	
Follow-Up (Day 58-62), n/N (%)	5/57 (8.8)	4/60 (6.7)	
Treatment Difference %	Not applicable		
95% CI	Not applicable		
p-value	Not applicable		
Prevalence of Azithromycin-Intermediate <i>S. pneumoniae</i> at each visit (minimum inhibitory concentration [MIC] 1.0mcg/mL)			
Baseline, n/N (%)	0/65	1/69 (1.4)	
End of Therapy (Day 12–16), n/N (%)	1/60 (1.7)	0/67	
Follow-Up (Day 58-62), n/N (%)	1/57 (1.8)	0/60	
Treatment Difference %	Not applicable		
95% CI	Not applicable		
p-value	Not applicable		
Prevalence of Azithromycin-Resistant <i>S. pneumoniae</i> at Each Visit (MIC ≥2.0mcg/mL)			
Baseline, n/N (%)	14/65 (21.5)	12/69 (17.4)	
End of Therapy (Day 12–16), n/N (%)	5/60 (8.3)	14/67 (20.9)	
Follow-Up (Day 58-62), n/N (%)	5/57 (8.8)	11/60 (18.3)	
Treatment Difference %	Not applicable		
95% CI	Not applicable		
p-value	Not applicable		
Secondary Outcome Variable(s):			
Prevalence of <i>H. influenzae</i> at Each Visit: ITT Population			
Baseline, n/N (%)	16/65 (24.6)	13/69 (18.8)	
End of Therapy (Day 12–16), n/N (%)	5/60 (8.3)	12/67 (17.9)	
Follow-Up (Day 58-62), n/N (%)	7/57 (12.3)	7/60 (11.7)	
Prevalence of Viridans Streptococci at Each Visit: ITT Population			
Baseline, n/N (%)	17/65 (26.2)	13/69 (18.8)	
End of Therapy (Day 12–16), n/N (%)	21/60 (35.0)	20/67 (29.9)	
Follow-Up (Day 58-62), n/N (%)	25/57 (43.9)	20/60 (33.3)	
Prevalence of <i>S. aureus</i> at Each Visit: ITT Population			
Baseline, n/N (%)	11/65 (16.9)	11/69 (15.9)	
End of Therapy (Day 12–16), n/N (%)	12/60 (20.0)	11/67 (16.4)	
Follow-Up (Day 58-62), n/N (%)	12/57 (21.1)	10/60 (16.7)	
Prevalence of Methicillin-Resistant <i>S. aureus</i> at Each Visit: ITT Population			
Baseline, n/N (%)	2/65 (3.1)	3/69 (4.3)	
End of Therapy (Day 12–16), n/N (%)	2/60 (3.3)	3/67 (4.5)	
Follow-Up (Day 58-62), n/N (%)	2/57 (3.5)	3/60 (5.0)	
Prevalence of <i>S. pneumoniae</i> Individual Serotypes at Each Visit: ITT Population			
Serotype			
All	Baseline, n/N (%)	33/65 (50.8)	30/69 (43.5)
	End of Therapy (Day 12–16), n/N (%)	9/60 (15.0)	20/67 (29.9)
	Follow-Up (Day 58-62), n/N (%)	11/57 (19.3)	15/60 (25.0)
00	Baseline, n/N (%)	3/65 (4.6)	0/69
	End of Therapy (Day 12–16), n/N (%)	0/60	0/67
	Follow-Up (Day 58-62), n/N (%)	0/57	0/60
01	Baseline, n/N (%)	0/65	0/69
	End of Therapy (Day 12–16), n/N (%)	0/60	0/67
	Follow-Up (Day 58-62), n/N (%)	1/57 (1.8)	0/60
03	Baseline, n/N (%)	0/65	1/69 (1.4)

	End of Therapy (Day 12–16), n/N (%)	0/60	1/67 (1.5)
	Follow-Up (Day 58-62), n/N (%)	0/57	1/60 (1.7)
06	Baseline, n/N (%)	11/65 (16.9)	10/69 (14.5)
	End of Therapy (Day 12–16), n/N (%)	3/60 (5.0)	6/67 (9.0)
	Follow-Up (Day 58-62), n/N (%)	5/57 (8.8)	4/60 (6.7)
10	Baseline, n/N (%)	1/65 (1.5)	0/69
	End of Therapy (Day 12–16), n/N (%)	0/60	0/67
	Follow-Up (Day 58-62), n/N (%)	0/57	0/60
11	Baseline, n/N (%)	1/65 (1.5)	2/69 (2.9)
	End of Therapy (Day 12–16), n/N (%)	0/60	1/67 (1.5)
	Follow-Up (Day 58-62), n/N (%)	0/57	0/60
14	Baseline, n/N (%)	5/65 (7.7)	2/69 (2.9)
	End of Therapy (Day 12–16), n/N (%)	2/60 (3.3)	1/67 (1.5)
	Follow-Up (Day 58-62), n/N (%)	2/57 (3.5)	1/60 (1.7)
15	Baseline, n/N (%)	0/65	1/69 (1.4)
	End of Therapy (Day 12–16), n/N (%)	0/60	1/67 (1.5)
	Follow-Up (Day 58-62), n/N (%)	0/57	0/60
18	Baseline, n/N (%)	0/65	0/69
	End of Therapy (Day 12–16), n/N (%)	0/60	1/67 (1.5)
	Follow-Up (Day 58-62), n/N (%)	0/57	0/60
19	Baseline, n/N (%)	8/65 (12.3)	6/69 (8.7)
	End of Therapy (Day 12–16), n/N (%)	2/60 (3.3)	4/67 (6.0)
	Follow-Up (Day 58-62), n/N (%)	2/57 (3.5)	3/60 (5.0)
23	Baseline, n/N (%)	3/65 (4.6)	8/69 (11.6)
	End of Therapy (Day 12–16), n/N (%)	2/60 (3.3)	5/67 (7.5)
	Follow-Up (Day 58-62), n/N (%)	1/57 (1.8)	6/60 (10.0)
Unknown	Baseline, n/N (%)	1/65 (1.5)	0/69
	End of Therapy (Day 12–16), n/N (%)	0/60	0/67
	Follow-Up (Day 58-62), n/N (%)	0/57	0/60
Clinical Response at End of Therapy: ITT Population			
Success, n/N (%)		45/65 (69.2)	50/69 (72.4)
Failure, n/N (%)		15/65 (23.0)	18/69 (26.0)
Missing, n/N (%)		5/65 (7.6)	1/69 (1.4)
Safety Population - Safety Results: Safety Population - Adverse events (AEs) and serious adverse events (SAEs) were collected after the start of the study (the time at which informed consent was obtained) until the Follow-Up visit (Day 58-62).			
	Amoxicillin / clavulanate 90/6.4mg/kg/day ES 600 (N=65)	Azithromycin (N=69)	
Most Frequent Adverse Events – On-Therapy or At Any Time During the Study	n (%)	n (%)	
Subjects with any AE(s), n (%)	56 (86.2)	50 (72.5)	
Otitis media	26 (40.0)	6 (8.7)	
Diarrhea	19 (29.2)	23 (33.3)	
Upper respiratory tract infection	18 (27.7)	8 (11.6)	
Rhinitis	12 (18.5)	2 (2.9)	
Conjunctivitis	7 (10.8)	4 (5.8)	
Dermatitis, contact	7 (10.8)	3 (4.3)	
Gastroenteritis	6 (9.2)	4 (5.8)	
Allergy	5 (7.7)	4 (5.8)	
Vomiting	4 (6.2)	3 (4.3)	
Injury	3 (4.6)	1 (1.4)	
Rash	3 (4.6)	1 (1.4)	
Pharyngitis	2 (3.1)	3 (4.3)	
Asthma	1 (1.5)	3 (4.3)	

Pneumonia	1 (1.5)	4 (5.8)
Serious Adverse Events (SAEs)- On-Therapy or At Any Time During the Study n (%) [n considered by the investigator to be related to study medication]		
	Amoxicillin / clavulanate 90/6.4mg/kg/day ES 600 (N=65)	Azithromycin (N=69)
	n (%) [related]	n (%) [related]
Subjects with non-fatal SAEs, n (%)	0	0
	n (%) [related]	n (%) [related]
Subjects with fatal SAEs, n (%)	0	0

Conclusion:

Amoxicillin/clavulanate and azithromycin differed in their effects on nasopharyngeal carriage of specific pathogens. The prevalence of *S. pneumoniae* in the amoxicillin/clavulanate and azithromycin treatment groups was 15.0% and 29.9%, respectively at end of therapy and 19.3% and 25.0%, respectively, at follow-up. Overall, approximately 70% of the subjects in each treatment group had clinical success in this study. AEs were reported by 86.2% of subjects in the amoxicillin/clavulanate group and 72.5% of subjects in the azithromycin group. The most frequently reported AEs were otitis media, diarrhea and upper respiratory tract infection in both treatment groups. No SAEs were reported.

Publications:

Acute otitis media in children: a study of nasopharyngeal carriage of potential pathogens and therapeutic efficacy of cefixime and amoxicillin-clavulanate. Boulesteix, J., Begue, P., Dubreuil, C., Megraud, F., Dabernat, H., Geslin, P., de La Rocque, F., and Trinh, A. *Infection* 95; 23 Suppl 2(S79-82)

Change in nasopharyngeal carriage of streptococcus pneumoniae resulting from antibiotic therapy for acute otitis media in children. Cohen, R., Bingen, E., Varon, E., de La Rocque, F., Brahimi, N., Levy, C., Boucherat, M., Langue, J., and Geslin, P. *Pediatr Infect Dis J* 97; 16(6):555-60

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