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Study No.: 555
Title: Evaluating the Impact of Amoxicillin/Clavulanate Potassium Therapy on Carriage of Susceptible and Resistant <i>Streptococcus pneumoniae</i> .
Rationale: The incidence of antibacterial resistance among respiratory tract pathogens, especially <i>S. pneumoniae</i> , is a significant problem, particularly among the pediatric population. This study was designed to evaluate the impact of amoxicillin/clavulanate potassium therapy on nasopharyngeal carriage of susceptible and resistant <i>S. pneumoniae</i> .
Phase: III
Study Period: 25 October 1999 to 19 May 2001.
Study Design: Randomized (1:1), parallel-group, single-blind, multicenter, comparative study. Subjects were seen at diagnosis/screening (day 1), end of treatment (days 12-16), first follow up (days 26-34) and second follow up (days 80-100).
Centers: 3 centers (United States).
Indication: Upper respiratory tract infection (URTI), including Acute Otitis Media (AOM) and Sinusitis
Treatment: Subjects were randomized to receive either amoxicillin/clavulanate ES-600 (14:1 formulation) 90/6.4 mg/kg a day in two equal doses given every 12 hours (bid) or amoxicillin/clavulanate (7:1 formulation) 45/6.4 mg/kg a day in two equal doses given every 12 hours. The volume of the dose for the subject's weight range was listed in a Recommended Dosing Chart provided by the sponsor. The doses were to be given immediately prior to food (i.e., breakfast and dinner). The subjects were instructed to attend the clinic for four visits: Diagnosis/Screening (Visit 1, Day 1), End of Therapy (Visit 2, Day 12-16), Follow up #1 (Visit 3, Day 26-34) and Follow up #2 (Visit 4, Day 80-100).
Objectives: The primary objective was to evaluate the impact of amoxicillin/clavulanate potassium therapy on rates of nasopharyngeal colonization by pneumococci, specifically investigating the impact of the variation of dosage. The secondary objectives were to compare the proportions of children colonized with non-susceptible pneumococci at 12--16, 26-34, and 80-100 days after diagnosis and start of treatment with amoxicillin/clavulanate (14:1) or amoxicillin/clavulanate (7:1) with the proportion found before treatment; and to elucidate the mechanisms whereby use of antibacterials may be associated with any change in the carriage of resistant pneumococci.
Primary Outcome/Efficacy Variable: The prevalence of nasopharyngeal carriage of pneumococci and changes in the prevalence of drug-resistant strains, comparing the results of nasopharyngeal cultures before therapy with the results of cultures obtained at selected intervals (approximately 15, 30, and 90 days) after the initiation of therapy.
Secondary Outcome/Efficacy Variable(s): Relative proportions of pneumococcal isolates that were susceptible and non-susceptible at selected intervals (approximately 15, 30, and 90 days). Prevalence of pneumococcal isolates with different susceptibility patterns or serotypes before, during, and after antibacterial therapy. Clinical response (success or failure) at the End of Therapy (EOT) visit (Day 12-16). Clinical success at EOT was defined as sufficient resolution of AOM such that no additional antibacterial therapy for AOM was indicated. Clinical failure was recorded when there was insufficient improvement of AOM at EOT requiring additional antibacterial therapy. Clinical failure at follow-up was defined as the inability to clear or improve the symptoms of AOM 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 in intent-to-treat (ITT) analyses.
Statistical Methods: The ITT population consisted of all subjects who received at least one dose of study medication. For analysis of bacteriology findings, the ITT population was restricted to those subjects from whose swab samples <i>S. pneumoniae</i> was cultured at Baseline. The Per-Protocol (PP) bacteriological population was a subset of the ITT bacteriological population that excluded subjects with specified protocol violations. 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 gender, aged 3 to 72 months with a diagnosis of upper respiratory tract infection (URTI), to include acute otitis media (AOM), defined as purulent otorrhea of less than 24 hours duration or at least two of the following: acute ear pain within the previous 24 hours; distinct fullness or bulging of the tympanic membrane; red, yellow, or white discoloration of the tympanic membrane; and opacification of the tympanic membrane; or sinusitis (defined as any two of the following: nasal discharge for 10 days or longer; daytime cough for 10 days or longer; and at

<p>least one of the following: headache, facial pain or swelling, tooth pain, fever, and malodorous breath). Subjects were not eligible for inclusion in the study if they had a history of allergy or intolerance to penicillins, cephalosporins, or other beta-lactam antibacterials; had received a systemic antibacterial within the previous 2 weeks; had 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/deficiency or immunosuppressive therapy; had received any investigational drug within the previous 30 days; had previously enrolled in this study; had phenylketonuria; had severe underlying disease; or were taking probenecid or other tubular secretion inhibitors.</p>		
	Amoxicillin / clavulanate 90/6.4mg/kg/day ES 600	Amoxicillin / clavulanate 45/6.4mg/kg/day (7:1)
Number of Subjects:		
Planned, N	200	200
Randomized, N	104*	98*
Diagnosis, n(%)		
AOM Only	97 (93.2)	95 (96.9)
Sinusitis Only	6 (5.8)	2 (2.0)
Both	1 (1.0)	1 (1.0)
Completed, n (%)	69 (66.3)	72 (73.5)
Total Number Subjects Withdrawn, n (%)	35 (33.7)	26 (26.5)
Withdrawn due to Adverse Events, n (%)	2 (1.9)	0
Withdrawn due to Lack of Efficacy, n (%)	Not available	Not available
Withdrawn for Other Reasons, n (%)	33 (31.7)	26 (26.5)
*The study was terminated early due to poor recruitment		
Demographics	Amoxicillin / clavulanate 90/6.4mg/kg/day ES 600	Amoxicillin / clavulanate 45/6.4mg/kg/day (7:1)
N (ITT)	104	98
Females: Males	49:55	59:39
Mean Age, months (SD)	27.6 (18.0)	28.4 (19.0)
White, n (%)	51 (49.0)	54 (55.1)
Primary Efficacy Results: Bacteriology PP with <i>S. pneumoniae</i> Population		
	Amoxicillin / clavulanate 90/6.4mg/kg/day ES 600	Amoxicillin / clavulanate 45/6.4mg/kg/day (7:1)
Prevalence of Nasopharyngeal <i>S. pneumoniae</i> at Each Visit		
Baseline (ITT), n/N (%)	39/104 (37.5)	43/98 (43.9)
End of Treatment (Day 12–16), n/N (%)	5/35 (14.3)	6/40 (15.0)
Follow-Up 1 (Day 26-34), n/N (%)	6/31 (19.4)	5/27 (18.5)
Follow-Up 2 (Day 80-100), n/N (%)	5/22 (22.7)	5/21 (23.8)
Treatment Difference %	Not applicable	
95% CI	Not applicable	
p-value	Not applicable	
Prevalence of Amoxicillin-Resistant <i>S. pneumoniae</i> at Each Visit		
End of Treatment (Day 12–16), n/N (%)	0/5	0/6
Follow-Up 1 (Day 26-34), n/N (%)	0/6	0/5
Follow-Up 2 (Day 80-100), n/N (%)	0/5	0/5
Treatment Difference %	Not applicable	
95% CI	Not applicable	
p-value	Not applicable	
Secondary Outcome Variable(s):		
	Amoxicillin / clavulanate 90/6.4mg/kg/day ES 600	Amoxicillin / clavulanate 45/6.4mg/kg/day (7:1)
Prevalence of Nasopharyngeal <i>S. pneumoniae</i> with Different Serotypes at Each Visit: ITT Population		
Subjects with <i>S. pneumoniae</i> at Baseline	n=39	n=43

<i>S. pneumoniae</i> at Post-Baseline Visit(s), n (%)	12 (30.8)	14 (32.6)
<i>S. pneumoniae</i> of Serotype Different to Baseline at Post-Baseline Visit(s), n (%)	8 (20.5)	10 (23.3)
Two strains of <i>S. pneumoniae</i> at Post-Baseline Visit(s), n (%)	3 (7.7)	1 (2.3)
Two strains of <i>S. pneumoniae</i> with Different Serotypes at Post-Baseline Visit(s), n (%)	1 (2.6)	0
Subjects without <i>S. pneumoniae</i> at Baseline	n=65	n=55
<i>S. pneumoniae</i> at End of Treatment, n (%)	3 (4.6)	3 (5.5)
<i>S. pneumoniae</i> at Follow-Up 1, n (%)	7 (10.8)	6 (10.9)
<i>S. pneumoniae</i> at Follow-Up 2, n (%)	8 (12.3)	11 (20.0)
Clinical Response at End of Therapy: Clinical PP with <i>S. pneumoniae</i> Population - AOM subjects only No clinical response data presented for sinusitis subjects, as only a few subjects with this diagnosis were enrolled into the study.		
	N=32	N=38
Success, n (%)	31 (96.8)	33 (86.8)
Failure, n (%)	1 (3.1)	5 (13.1)
Safety Results: Safety Population - Adverse events (AEs) were collected after the start of the study (the time at which informed consent was obtained) until the Follow-Up visit (Day 80-100). Serious adverse events (SAEs) were reported that occurred during the clinical trial or within 30 days (or five half-lives, whichever was longer) of receiving the last dose of study medication.		
	Amoxicillin / clavulanate 90/6.4mg/kg/day ES 600 (N=104)	Amoxicillin / clavulanate 45/6.4mg/kg/day (7:1) (N=98)
Most Frequent Adverse Events (AEs) – On-Therapy or At Any Time During the Study	n (%)	n (%)
Subjects with any AE(s), n (%)	58 (55.8)	49 (50.0)
Otitis media	32 (30.8)	23 (23.5)
Upper respiratory tract infection	15 (14.4)	12 (12.2)
Fever	12 (11.5)	13 (13.3)
Asthma	6 (5.8)	3 (3.1)
Coughing	5 (4.8)	4 (4.1)
Diarrhea	5 (4.8)	3 (3.1)
Gastroenteritis	5 (4.8)	6 (3.1)
Rash	5 (4.8)	1 (1.0)
Injury	4 (3.8)	1 (1.0)
Dermatitis, contact	3 (2.9)	5 (5.1)
Infection, viral	3 (2.9)	2 (2.0)
Pharyngitis	3 (2.9)	7 (7.1)
Earache	2 (1.9)	6 (6.1)
Vomiting	1 (1.0)	3 (3.1)
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=104)	Amoxicillin / clavulanate 45/6.4mg/kg/day (7:1) (N=98)
	n (%) [related]	n (%) [related]
Subjects with non-fatal SAEs, n (%)	2 (1.9) [0]	2 (2.0) [0]
Fever	1 (1.0) [0]	0
Otitis media	1 (1.0) [0]	0
Gastroenteritis	0	2 (2.0) [0]
	n (%) [related]	n (%) [related]
Subjects with fatal SAEs, n (%)	0	0

Conclusion:

Approximately 40% of the young children having a diagnosis of acute otitis media or sinusitis were carriers of nasopharyngeal *S. pneumoniae* at baseline. Both treatment groups showed a reduction in the rate of nasopharyngeal carriage of *S. pneumoniae* from Baseline to End of Treatment (from 37.5% to 14.3% in the amoxicillin/clavulanate ES-600 group and from 43.9% to 15.0% in the amoxicillin/clavulanate (7:1) group, in the PP population. At the first Follow-Up (Day 26-34), the rate of carriage was still reduced from Baseline (approximately 19% for both treatment groups) and at the second Follow-Up (Day 80-100), the carriage rate increased slightly (to approximately 23% in both treatment groups) but remained below Baseline. In a majority of these cases, the pneumococci isolated at the subsequent visit(s) were of different serotype than the strain isolated at baseline. Neither treatment group showed any occurrence of amoxicillin-resistant *S. pneumoniae* after antibacterial therapy.

AEs were reported by 58 (55.8%) subjects in the amoxicillin/clavulanate ES-600 group and 49 (50.0%) subjects in the amoxicillin/clavulanate (7:1) group. The most frequently reported AEs were otitis media, upper respiratory tract infection, and fever in both treatment groups. SAEs were reported by 1.9% of subjects in the amoxicillin/clavulanate ES-600 group and 2.0% of subjects in the amoxicillin/clavulanate (7:1) group. No fatal SAEs were reported.

The findings of this study suggest that any of the three proposed mechanisms for increasing the prevalence of non-susceptible *S. pneumoniae* after antibacterial therapy (new colonization, selection, and mutation of existing strains) are possible, but they do not support any one mechanism as more likely than any other. Although this study was not designed primarily to measure efficacy, both treatments showed a high clinical success rate in patients with a baseline diagnosis of AOM.

Publications:

No Publication

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