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Study No.: 325
Title: A comparison of the efficacy, safety and tolerability of Augmentin tid 20/5 mg/kg/day po versus Augmentin bid 25/3.6 mg/kg/day po in the treatment of acute bacterial lower respiratory tract infections in children.
Rationale: At the time of this study, amoxicillin/clavulanate was dosed at 20/5 mg/kg/day orally (po) in divided doses three times a day (tid). A twice daily (bid) administration would avoid the need for lunch-time dosing. This study was to determine if the administration of amoxicillin/clavulanate 25/3.6 mg/kg/day in two divided doses was no more than 10% less effective than the established regimen for the treatment of lower respiratory tract infections (RTIs) in children. The change in dosage was supported by microbiological and human data.
Phase: IIIb
Study Period: 1 November 1993 to 24 June 1994.
Study Design: A prospective, single-blind (blind to investigator), randomised, parallel-group, comparative, multicenter study.
Centres: 26 centres in the United Kingdom.
Indication: Acute bacterial lower respiratory tract infections (RTIs).
Treatment: Subjects were randomized to one of two treatments in a 1:1 ratio for 7 days: Amoxicillin/clavulanate 4:1 suspension formulation (250/62 mg per 5 mL) based on a total daily dose of 20 mg/kg/day amoxicillin plus 5 mg/kg/day clavulanic acid, given in accordance with body weight up to 18 kg, then at a fixed dose of 5 mL, tid. (amoxicillin:clavulanate 7:1) Amoxicillin/clavulanate 7:1 suspension formulation (400/57 mg per 5mL) based on a total daily dose of 25 mg/kg/day amoxicillin plus 3.6 mg/kg/day clavulanic acid, dosed at 0.156 mL/kg bid. Subjects were instructed to attend the clinic four times during the study: Screening visit (Visit 1, Day 0), On-Therapy visit (Visit 2, Day 3-5), End of Therapy visit (Visit 3, Day 12-16) and Follow Up (Visit 4, Day 28-42)
Objectives: The primary objective was to compare the efficacy of a regimen based on amoxicillin/clavulanate tid 20/5 mg/kg/day po versus amoxicillin/clavulanate bid 25/3.6 mg/kg/day po in the treatment of bacterial lower RTIs in children
Primary Outcome/Efficacy Variable: Clinical response (success or failure) at follow-up (Visit 4). Clinical success was defined as sufficient resolution of lower RTI such that no additional antibacterial therapy for lower RTI was indicated. Clinical failure at follow up was defined as reappearance or deterioration of lower RTI following clinical success at end of therapy. If a subject was deemed to be a clinical failure at any stage, this outcome was carried forward to all further visits
Secondary Outcome/Efficacy Variable(s): Clinical outcome at follow-up (Visit 4), signs and symptoms of infection, global assessment of disease state and sputum evaluation. The analysis of bacteriological sputum data was not performed because of too few bacteriological data. A comparison of the incidence of protocol defined diarrhea (PDD) was performed. Protocol defined diarrhea (PDD) was defined as three or more watery stools in one day or two or more watery stools per day for two consecutive days during Days 1-11, as recorded in patient diaries. Additionally, any event of diarrhea noted by the investigator as an adverse event was included as a PDD event in this analysis, even if not recorded in patient diaries.
Statistical Methods: The Intent-to-Treat (ITT) population included all randomized subjects. The Per-Protocol (PP) population included subjects without protocol deviations that were considered to bias the efficacy assessments. Safety was evaluated in the ITT population. For the primary binary variables, linear logistic regression models were used to assess treatment, centre and treatment centre interaction effects. Assessments of equivalence for proportions were made using two-sided 95% confidence intervals (CIs) based on the normal distribution approximation to the binomial distribution. Tests of proportions in contingency tables were made using chi-square test, or Fischer's exact test where expected cell frequencies were small. All statistical tests were carried out using two-tailed tests and a significance level of 5% was used to determine whether or not to regard the result as statistically significant. Tests of interactions, however, were regarded as statistically significant at the 10% level. The bid group was considered as effective as the tid group if the lower limit of the confidence interval was not below -10%.
Study Population: Subjects aged 2 to 12 years with acute bacterial lower RTIs, presenting with at least two of the following signs and symptoms: high fever, abrupt onset or sudden deterioration in a mild respiratory illness, productive cough, shortness of breath, respiratory crepitation, or wheeze. Subjects with known or suspected localised lung disease of any kind, subjects with a lower RTI sufficiently severe as to require intravenous therapy or hospital

admission, and subjects with a concomitant infection were excluded.		
	Amoxicillin/clavulanate 20/5 mg/kg/day tid	Amoxicillin/clavulanate 25/3.6 mg/kg/day bid
Number of Subjects:		
Planned, N	180	180
Randomised, N	216	221
Completed, n (%)	171 (79.2)	182 (82.4)
Total Number Subjects Withdrawn, n (%)	45 (20.8)	39 (17.6)
Withdrawn due to Adverse Events, n (%)	13 (6.0)	6 (2.7)
Withdrawn due to Lack of Efficacy, n (%)	3 (1.4)	3 (1.4)
Withdrawn for Other Reasons, n (%)	29 (13.4)	30 (13.6)
Demographics		
	Amoxicillin/clavulanate 20/5 mg/kg/day tid	Amoxicillin/clavulanate 25/3.6 mg/kg/day bid
N (ITT)	216	221
Females: Males	100: 116	118: 103
Mean Age, years (SD)	5.5 (2.9)	5.1 (2.9)
Caucasian, n (%)	210 (97.2)	215 (97.3)
Primary Efficacy Results:		
	Amoxicillin/clavulanate 20/5 mg/kg/day tid (N=216)	Amoxicillin/clavulanate 25/3.6 mg/kg/day bid (N=221)
Clinical response at follow-up: (ITT Population)		
Success, n (%)	168 (77.8)	179 (81.0)
Failure, n (%)	48 (22.2)	42 (19.0)
Treatment difference (bid-tid) %	3.2	
95% CI	-4.36, 10.80	
p-value	Not available	
Secondary Outcome Variable(s):		
	Amoxicillin/clavulanate 20/5 mg/kg/day tid (N=216)	Amoxicillin/clavulanate 25/3.6 mg/kg/day bid (N=221)
Clinical outcome at follow-up: (ITT Population)		
Clinical cure, n (%)	168 (77.8)	179 (81.0)
Failure, n (%)	7 (3.2)	6 (2.7)
Failure at Visit 2, n (%)	1 (0.5)	4 (1.8)
Relapse, n (%)	9 (4.2)	5 (2.3)
Indeterminate, n (%)	24 (11.1)	19 (8.6)
Lost subjects, n (%)	7 (3.2)	8 (3.6)
Signs and symptoms of infection: (ITT Population)		
Signs and symptoms at end of therapy		
Fever, n (%)	2 (0.9)	3 (1.4)
Productive cough, n (%)	10 (4.6)	10 (4.5)
Respiratory crepitation, n (%)	5 (2.3)	0
Wheeze, n (%)	10 (4.6)	12 (5.4)
Shortness of breath, n (%)	4 (1.9)	3 (1.4)
No signs/symptoms, n (%)	185 (85.6)	190 (86.0)
Signs and symptoms at follow-up		
Fever, n (%)	0	0
Productive cough, n (%)	9 (4.2)	6 (2.7)
Respiratory crepitation, n (%)	4 (1.9)	2 (0.9)
Wheeze, n (%)	7 (3.2)	7 (3.2)
Shortness of breath, n (%)	4 (1.9)	3 (1.4)
No signs/symptoms, n (%)	193 (89.4)	198 (89.6)
Global assessment of disease state: (ITT Population)		

Baseline assessment		
Mild, n (%)	50 (23.1)	52 (23.5)
Moderate, n (%)	158 (73.1)	165 (74.7)
Severe, n (%)	8 (3.7)	4 (1.8)
End of therapy assessment		
Absent, n (%)	184 (85.2)	193 (87.3)
Mild, n (%)	14 (6.5)	13 (5.9)
Moderate, n (%)	6 (2.8)	5 (2.3)
Severe, n (%)	0	0
Follow-up assessment		
Absent, n (%)	191 (88.4)	196 (88.7)
Mild, n (%)	10 (4.6)	8 (3.6)
Moderate, n (%)	6 (2.8)	4 (1.8)
Severe, n (%)	0	0
Sputum evaluation: (ITT Population, subjects with sputum data)		
End of therapy assessment, N	10	10
Sputum infrequent, n (%)	8 (80.0)	8 (80.0)
Sputum frequent, n (%)	2 (20.0)	2 (20.0)
Appearance clear, n (%)	2 (20.0)	5 (50.0)
Appearance mucoid, n (%)	2 (20.0)	2 (20.0)
Appearance purulent, n (%)	1 (10.0)	0
Appearance unknown, n (%)	5 (50.0)	3 (30.0)
Follow-up assessment, N	8	8
Sputum infrequent, n (%)	7 (87.5)	6 (100)
Sputum frequent, n (%)	1 (12.5)	0
Appearance clear, n (%)	4 (50.0)	4 (66.7)
Appearance mucoid, n (%)	1 (12.5)	0
Appearance purulent, n (%)	1 (12.5)	1 (16.7)
Appearance unknown, n (%)	2 (25.0)	1 (16.7)
Safety Results (ITT Population): On-therapy adverse events (AEs) were defined as AEs starting on or after Day 0, up to and including those starting on the last day of study medication. Serious adverse events (SAEs) were recorded on-therapy and within 30 days of receiving the last dose of study treatment.		
	Amoxicillin/clavulanate 20/5 mg/kg/day tid (N=216)	Amoxicillin/clavulanate 25/3.6 mg/kg/day bid (N=221)
Most Frequent Adverse Events – On-Therapy plus 30 Days Post-therapy	n (%)	n (%)
Subjects with any AE(s), n (%)	102 (47.2)	100 (45.2)
Vomiting	12 (5.6)	18 (8.1)
Rhinitis	20 (9.3)	17 (7.7)
Diarrhoea	13 (6.0)	15 (6.8)
Pharyngitis	7 (3.2)	12 (5.4)
Otitis media	14 (6.5)	7 (3.2)
Cervical lymphadenopathy	5 (2.3)	7 (3.2)
Asthma	12 (5.6)	5 (2.3)
Eczema	2 (0.9)	5 (2.3)
Coughing	7 (3.2)	4 (1.8)
Upper respiratory tract infection	5 (2.3)	4 (1.8)
Respiratory disorder	6 (2.8)	1 (0.5)
	Amoxicillin/clavulanate 20/5 mg/kg/day tid (N=216)	Amoxicillin/clavulanate 25/3.6 mg/kg/day bid (N=221)
Diarrhea, n (%)	9 (4.3)	6 (2.7)
95% C.I.	-5.0%, 2.0%	

Serious Adverse Events (SAEs) - On-Therapy plus 30 Days Post-therapy n (%) [n considered by the investigator to be related to study medication]		
	Amoxicillin/clavulanate 20/5 mg/kg/day tid (N=216)	Amoxicillin/clavulanate 25/3.6 mg/kg/day bid (N=221)
Subjects with non-fatal SAEs, n (%)	3 (1.4)	1 (0.5)
	n (%) [related]	n (%) [related]
Fever convulsions	0	1 (0.5) [0]
Abdominal pain	1 (0.5) [0]	0
Arthrosis	1 (0.5) [0]	0
Asthma	1 (0.5) [0]	0
Constipation	1 (0.5) [0]	0
Subjects with fatal SAEs, n (%)	0	0

Conclusion:

Amoxicillin/clavulanate, administered either as tid 20/5mg/kg/day or bid 25/3.6mg/kg/day, was effective in the treatment of bacterial lower respiratory tract infections in a paediatric population. The twice daily dosing regimen was shown to be as effective as the established regimen of dosing three times daily. The incidence of protocol defined diarrhea was low, and there was no statistically significant difference in incidence between the two groups. In the amoxicillin/clavulanate tid group, 102 (47.2%) subjects reported AEs and, in the amoxicillin/clavulanate bid group, 100 (45.2%) subjects reported AEs. The most frequently reported AEs were rhinitis, otitis media, and diarrhoea in the amoxicillin/clavulanate tid group and vomiting, rhinitis, and diarrhoea in the amoxicillin/clavulanate bid group. SAEs were reported by 3 subjects in the amoxicillin/clavulanate tid group, and 1 subject in the amoxicillin/clavulanate bid group; no SAEs were reported in more than one subject. No fatal SAEs were reported.

Publications:

Efficacy of twice-daily amoxycillin/clavulanate ('augmentin-duo' 400/57) in mild to moderate lower respiratory tract infection in children. Cook, R. C., Zachariah, J., Cree, F., and Harrison, H. E. Br J Clin Pract 96; 50(3):125-8

Efficacy of Twice-Daily Dosing of Augmentin in Acute Otitis Media in Children, Behre, U, MD; Buirow, H M, MD; Quinn, P, MD; Cree, F, MD; Harrison, H E, MD. Hauptstrasse Kehl, Germany; Sligo Health Centre, Sligo, Eire; SmithKline Beecham, Harlow, England; Hong Kong; China. 7th International Congress for Infectious Diseases. 6/10/1996

Date Updated: 08-Aug-2005