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<b>Study No.:</b> 311
<b>Title:</b> A comparison of the efficacy, safety and tolerability of <i>Augmentin</i> 60/15 mg/kg/day (4:1 ratio) given po in three divided doses versus <i>Augmentin</i> <sup>TM</sup> 70/10 mg/kg/day (7:1 ratio) given po in two divided doses in the treatment of children with acute otitis media.
<i>Augmentin</i> is a registered trademark of the GlaxoSmithKline group of companies.
<b>Rationale:</b> The paediatric dosing regimen for amoxicillin/clavulanate in acute otitis media (AOM) in a number of European countries at the time of this study was 60/15 mg/kg/day (4:1 ratio) given orally in three divided doses three times a day (tid). A twice daily dosing regimen is preferable in pediatric subjects, eliminating the need for lunch time dosing. The current study was designed to compare the efficacy, safety and tolerability of the two regimens to determine whether the newly proposed regimen was no more than 10% less effective than the established regimen.
<b>Phase:</b> IIIB
<b>Study Period:</b> 5 November 1993 to 15 June 1994.
<b>Study Design:</b> A prospective, single-blind (blind to investigator), randomised, parallel-group, multicenter, comparative study. Subjects were instructed to attend the clinic for the following scheduled visits: Visit 1, Screening (Day 0); Visit 2, on-therapy (Day 3-5); Visit 3, end-of-therapy (Day 10-17); Visit 4, follow-up (Day 28-42).
<b>Centres:</b> 26 active centres in 5 countries (Belgium [5], Germany [7], Ireland [4], Switzerland [7] and UK [3]).
<b>Indication:</b> Acute otitis media.
<b>Treatment:</b> Subjects were randomised in a 1:1 ratio to one of two treatment groups for 10 days of treatment: Amoxicillin/clavulanate 60/15 (a '250/62 per 5 mL' suspension) given as a fixed dose (5 ml for subjects weighing 12-23 kg; 10 mL for subjects weighing 24-20 kg) tid or Amoxicillin/clavulanate 70/10 (a '400/57 per 5 mL' suspension) given in accordance with body weight up to 23 kg (0.44 mL/kg), then as a fixed dose (10 mL) bid.
<b>Objectives:</b> The primary objective was to compare the clinical efficacy of amoxicillin/clavulanate 60/15 mg/kg/day given orally (po) in three divided doses with that of amoxicillin/clavulanate 70/10 mg/kg/day given po in two divided doses in the treatment of children with AOM.
<b>Primary Outcome/Efficacy Variable:</b> Clinical response (success or failure) at the end of therapy (Visit 3) and at follow-up (Visit 4). Clinical success at 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 end of therapy requiring additional antibacterial therapy. Clinical failure at follow up was defined as reappearance or deterioration of AOM 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.
<b>Secondary Outcome/Efficacy Variable(s):</b> Clinical outcome at end of therapy and follow-up; signs and symptoms of AOM. Clinical outcomes were classified as clinical cure (complete or partial resolution of signs and symptoms of AOM, exclusive of middle ear effusion, within 72 hours of onset of therapy, and child has remained well up to this visit); relapse (after complete or partial resolution at visit 2, signs and symptoms of AOM reappeared) or clinical response indeterminate (unevaluable due to poor subject cooperation or extenuating circumstances). Bacteriological variables were defined but too few data were available for analysis. Bowel habit assessment included the incidence of protocol defined diarrhea (PDD), which was defined as three or more watery stools in one day (one day of PDD) or two watery stools per day for two consecutive days (two days of PDD).
<b>Statistical Methods:</b> The intent-to-treat (ITT) population included all randomised subjects. The safety population was identical to the ITT population. PDD was assessed in those subjects from the ITT population that returned diary cards. Assessments of equivalence for proportions were made using two-sided 95% confidence intervals (CIs) based on the normal distribution approximation to the binomial distribution for the difference in response rates (bid – tid). The bid treatment group was considered as effective as the tid group if the lower limit of the 95% CI was not below -10%. It should be noted that the study was not designed to demonstrate non-inferiority/equivalence for secondary end-points where the numbers of subjects was too small to draw any conclusions.
<b>Study Population:</b> Subjects aged between 2 and 12 years with a clinical diagnosis of AOM evidenced either by the visual appearance of the tympanic membrane (i.e. redness, bulging, loss of light reflex, rupture) or, by the presence of middle ear effusion (as demonstrated by otoscopy). The diagnosis was to be accompanied by at least two of the following signs and symptoms: Specific signs and symptoms: Ear pain, eye discharge, hearing loss.

Non-specific signs and symptoms: Fever, lethargy, irritability, anorexia, vomiting, diarrhoea. Subjects with a history of prolonged middle ear effusion (MEE), concomitant treatment with systemic steroids, decongestants or antihistamines, or concomitant infection were excluded.		
	<b>Amoxicillin/clavulanate 60/15 mg/kg/day tid</b>	<b>Amoxicillin/clavulanate 70/10 mg/kg/day bid</b>
Number of Subjects:		
Planned, N	360	
Randomised, N	232	231
Completed, n (%)	188 (81.0)	197 (85.3)
Total Number Subjects Withdrawn, n (%)	44 (19.0)	34 (14.7)
Withdrawn due to Adverse Events, n (%)	21 (9.1)	13 (5.6)
Withdrawn due to Lack of Efficacy, n (%)	5 (2.2)	5 (2.2)
Withdrawn for Other Reasons, n (%)	18 (7.8)	16 (6.9)
<b>Demographics</b>	<b>Amoxicillin/clavulanate 60/15 mg/kg/day tid</b>	<b>Amoxicillin/clavulanate 70/10 mg/kg/day bid</b>
N (ITT)	232	231
Females: Males	109: 123	122: 109
Mean Age, years (SD)	4.6 (2.3)	4.3 (2.1)
Caucasian, n (%)	230 (99.1)	231 (100)
<b>Treatment Compliance</b>		
Proportion of subjects with at least 80% compliance	72.8%	83.1%
Treatment difference (bid-tid)		10.3%
95% CI		2.78, 17.76
<b>Primary Efficacy Results: (ITT Population)</b>		
	<b>Amoxicillin/clavulanate 60/15 mg/kg/day tid (N=232)</b>	<b>Amoxicillin/clavulanate 70/10 mg/kg/day bid (N=231)</b>
Clinical response at end of therapy		
Success, n (%)	210 (90.5)	212 (91.8)
Failure, n (%)	22 (9.5)	19 (8.2)
Treatment difference (bid – tid)	1.3	
95% CI	-3.92, 6.43	
Clinical response at follow-up		
Success, n (%)	180 (77.6)	185 (80.1)
Failure, n (%)	55 (22.4)	46 (19.9)
Treatment difference (bid – tid)	2.5	
95% CI	-4.94, 9.94	
<b>Secondary Outcome Variable(s): (ITT population)</b>		
	<b>Amoxicillin/clavulanate 60/15 mg/kg/day tid (N=232)</b>	<b>Amoxicillin/clavulanate 70/10 mg/kg/day bid (N=231)</b>
Clinical outcome at end of therapy		
Clinical cure, n (%)	210 (90.5)	212 (91.8)
Failure at Visit 2, n (%)	4 (1.7)	1 (0.4)
Relapse, n (%)	4 (1.7)	6 (2.6)
Indeterminate, n (%)	4 (1.7)	1 (0.4)
'Lost' subjects, n (%)	10 (4.3)	11 (4.8)
Clinical outcome at follow-up		
Clinical cure, n (%)	180 (77.6)	185 (80.1)
Failure at Visit 2, n (%)	4 (1.7)	1 (0.4)
Relapse at Visit 3, n (%)	4 (1.7)	6 (2.6)
Recurrence, n (%)	14 (6.0)	18 (7.8)
Indeterminate, n (%)	11 (4.7)	10 (4.3)
'Lost' subjects, n (%)	19 (8.2)	11 (4.8)
Specific signs and symptoms of AOM at end of therapy		

Redness of drum, n (%)	17 (7.3)	19 (8.2)
Bulging, n (%)	8 (3.4)	5 (2.2)
Loss of light reflex, n (%)	24 (10.3)	18 (7.8)
Rupture of drum, n (%)	2 (0.9)	0
Ear pain, n (%)	3 (1.3)	5 (2.2)
Ear discharge, n (%)	1 (0.4)	0
Hearing loss, n (%)	5 (2.2)	3 (1.3)
Specific signs and symptoms of AOM at follow-up		
Redness of drum, n (%)	14 (6.0)	7 (3.0)
Bulging, n (%)	2 (0.9)	4 (1.7)
Loss of light reflex, n (%)	13 (5.6)	9 (3.9)
Rupture of drum, n (%)	2 (0.9)	1 (0.4)
Ear pain, n (%)	8 (3.4)	5 (2.2)
Ear discharge, n (%)	0	0
Hearing loss, n (%)	3 (1.3)	1 (0.4)
Non-specific signs and symptoms of AOM at end of therapy		
Fever, n (%)	2 (0.9)	1 (0.4)
Irritability, n (%)	2 (0.9)	0
Lethargy, n (%)	1 (0.4)	2 (0.9)
Anorexia, n (%)	1 (0.4)	0
Vomiting, n (%)	0	0
Diarrhoea, n (%)	0	0
No signs/symptoms, n (%)	229 (98.7)	228 (98.7)
Non-specific signs and symptoms of AOM at follow-up		
Fever, n (%)	4 (1.7)	6 (2.6)
Irritability, n (%)	3 (1.3)	1 (0.4)
Lethargy, n (%)	2 (0.9)	2 (0.9)
Anorexia, n (%)	1 (0.4)	1 (0.4)
Vomiting, n (%)	0	0
Diarrhoea, n (%)	0	0
No signs/symptoms, n (%)	225 (97.0)	224 (97.0)
<b>Bowel Habits – Incidence of PDD</b>		
	<b>Amoxicillin/clavulanate 60/15 mg/kg/day tid (N=224)</b>	<b>Amoxicillin/clavulanate 70/10 mg/kg/day bid (N=224)</b>
Diarrhea, n(%)	23 (10.3)	15 (6.7)
95% C.I. (bid-tid)	-8.7%, 1.6%	
<b>Safety Results: ITT Population</b> –Adverse events (AEs) were recorded at every visit after screening. Any serious adverse event (SAE) which occurred during the study or within 30 days of receiving the last dose of study medication was reported.		
	<b>Amoxicillin/clavulanate 60/15 mg/kg/day tid (N=232)</b>	<b>Amoxicillin/clavulanate 70/10 mg/kg/day bid (N=231)</b>
<b>Most Frequent Adverse Events – On-Therapy plus 30 Days Post-Therapy</b>	<b>n (%)</b>	<b>n (%)</b>
Subjects with any AE(s), n (%)	94 (40.5)	111 (48.1)
Bronchitis	14 (6.0)	14 (6.1)
Rhinitis	17 (7.3)	13 (5.6)
Vomiting	10 (4.3)	12 (5.2)
Diarrhoea	12 (5.2)	10 (4.3)
Pharyngitis	8 (3.4)	10 (4.3)
Coughing	9 (3.9)	8 (3.5)
Viral infection	2 (0.9)	7 (3.0)
Erythematous rash	2 (0.9)	7 (3.0)
Respiratory disorder	8 (3.4)	5 (2.2)

Conjunctivitis	3 (1.3)	5 (2.2)
Bacterial infection	2 (0.9)	5 (2.2)
Eczema	1 (0.4)	5 (2.2)
Fever	4 (1.7)	4 (1.7)
Moniliasis	6 (2.6)	3 (1.3)
Abdominal pain	4 (1.7)	3 (1.3)
Ear disorder, not otherwise specified	10 (4.3)	2 (0.9)
<b>Serious Adverse Events - On-Therapy plus 30 Days Post-Therapy</b>		
<b>n (%) [n considered by the investigator to be related to study medication]</b>		
	<b>Amoxicillin/clavulanate 60/15 mg/kg/day tid (N=232)</b>	<b>Amoxicillin/clavulanate 70/10 mg/kg/day bid (N=231)</b>
Subjects with non-fatal SAEs, n (%)	2 (0.9)	0
	<b>n (%) [related]</b>	<b>n (%) [related]</b>
Abdominal pain	1 (0.4) [1]	0
Diarrhoea	2 (0.9) [1]	0
Vomiting	1 (0.4) [0]	0
Subjects with fatal SAEs, n (%)	0	0

**Conclusion:**

Amoxicillin/clavulanate, administered either tid or bid, was effective in the treatment of acute otitis media in children. The regimen of a 7:1 ratio of amoxicillin:clavulanic acid given twice daily was shown to be as effective as the established regimen of a 4:1 ratio of amoxicillin:clavulanic acid given three times daily, and compliance with taking study medication was significantly better in subjects receiving the bid regimen than in those receiving the tid regimen. The incidence of protocol defined diarrhea was lower in the amoxicillin clavulanate bid group than in the amoxicillin clavulanate tid group, although the differences between the groups in the overall incidence of protocol defined diarrhea did not reach clinical significance. Adverse events were reported in 94 (40.5%) of the tid group, and 111 (48.1%) of the bid group, with rhinitis, and bronchitis being the most frequently reported in both groups. Serious adverse events were reported in 2 subjects in the tid group, with diarrhoea being reported by both those subjects. No fatal SAEs were reported.

**Publications:**

Evaluation of amoxicillin clavulanate twice daily versus thrice daily in the treatment of otitis media in children. danish-swedish study group. Jacobsson, S., Fogh, A., Larsson, P., and Lomborg, S. Eur J Clin Microbiol Infect Dis 93; 12(5):319-24

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