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<b>Study No.:</b> 330
<b>Title:</b> A comparison of the efficacy, safety and tolerability of Augmentin 30/7.5 mg/kg/day po given in three divided doses (4:1 ratio) versus Augmentin 35/5 mg/kg/day po given in two divided doses (7:1 ratio) in the treatment of children with recurrent tonsillitis.
<b>Rationale:</b> At the time of this study, the dosing regimen for amoxicillin/clavulanate for tonsillitis was based on 30/7.5 mg/kg/day three times a day (tid). However, a clinical programme was undertaken to evaluate a twice daily (bid) dosing regimen based on 35/5 mg/kg/day. This study was designed to determine whether the administration of amoxicillin/clavulanate 35/5 mg/kg/day bid was no less than 10% clinically effective compared to the standard 30/7.5 mg/kg/day dosing regimen in the treatment of recurrent tonsillitis. The proposed change in regimen was supported by pharmacokinetic, microbiological and in vivo animal data.
<b>Phase:</b> IIIb
<b>Study Period:</b> 5 October 1994 to 24 April 1995.
<b>Study Design:</b> An observer-blinded, randomised, parallel group, comparative, multi-center study. Patients were assessed before (Visit 1, Day 0), during (Visit 2, Day 4±1) and at the end of treatment (Visit 3, Day 14±2), and at a follow up assessment, 35±7 days from the start of treatment.
<b>Centres:</b> A total of 35 centres in: Germany (9), Ireland (17), Italy (7) and The Netherlands (2).
<b>Indication:</b> Recurrent tonsillitis.
<b>Treatment:</b> Subjects were randomised to one of two treatments in a 1:1 ratio for a total of 10 days: Amoxicillin/clavulanate 250 mg/62 mg pediatric suspension: each 5 ml containing amoxicillin 250 mg as the trihydrate and clavulanic acid 62 mg as the potassium salt (amoxicillin:clavulanate 4:1). The treatment was based on a total daily dose of 30 mg/kg/day amoxicillin plus 7.5 mg/kg/day clavulanic acid, given as a fixed dose of either 2.5 or 5.0 mL tid. Amoxicillin/clavulanate 400 mg/57 mg pediatric suspension: each 5 ml containing amoxicillin 400mg as the trihydrate and clavulanic acid 57 mg as the potassium salt (amoxicillin:clavulanate 7:1). The treatment was based on a total daily dose of 35 mg/kg/day amoxicillin plus 5 mg/kg/day clavulanic acid, dosed at 0.22 mL/kg bid in accordance with body weight from 12 kg to 23 kg, and for weights higher than 23 kg, at a fixed dose bid of 5 mL. Subjects were instructed to attend the clinic four times during the study: at the Screening visit (Visit 1, Day 0), On-Therapy visit (Visit 2, Day 3-5), End of Therapy visit (Visit 3, Day 12-14), and Follow Up visit (Visit 4, Day 28-42).
<b>Objectives:</b> The primary objective was to compare the clinical efficacy of amoxicillin/clavulanate 30/7.5 mg/kg/day po given in three divided doses with that of amoxicillin/clavulanate 35/5 mg/kg/day po given in two divided doses in the treatment of children with an episode of recurrent tonsillitis. The secondary objectives were to compare the safety and tolerability of the two treatment regimens with particular reference to bowel habit; and to compare the microbial eradication of pathogens by amoxicillin/clavulanate 30/7/5mg/kg/day po given tid with that of amoxicillin/clavulanate 35/5/mg/kg/day po given bid, in the treatment of children with an episode of recurrent tonsillitis.
<b>Primary Outcome/Efficacy Variable:</b> Clinical response (success or failure) to study medications at the end of therapy (Visit 3). Clinical success was defined as sufficient resolution of tonsillitis such that no additional antibacterial therapy for tonsillitis was indicated. Clinical failure was recorded when there was insufficient improvement of tonsillitis at end of therapy requiring additional antibacterial therapy.
<b>Secondary Outcome/Efficacy Variable(s):</b> Incidence of recurrence of tonsillitis at or prior to the scheduled follow-up visit (Visit 4); Group A Beta-Haemolytic Streptococci (GABHs)/primary pathogens bacteriological outcome at end of therapy (Visit 3) and follow-up (Visit 4); GABHs/primary pathogens bacteriological response at end of therapy (Visit 3) and follow-up (Visit 4); Relationship between the presence/absence of GABHs/primary pathogens and presence/absence of beta-lactamase producers; Emergence of new organisms at Visit 3 and 4 (colonization/superinfection); Global clinical response; Signs and symptoms of tonsillitis; Time to return to normal temperature. A comparison of the incidence of protocol defined diarrhea (PDD) was also performed. PDD 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). In addition, 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.

<p><b>Statistical Methods:</b> All randomised subjects were included in the intent-to-treat (ITT) population. Subjects who were lost to follow up were included in the analysis as treatment failures if there was no information to the contrary. The ITT bacteriology population comprised all subjects in the ITT population, who had at least one pathogen isolated from the tonsil swab taken at Visit 1. Safety was assessed using the ITT population.</p> <p>Assessments of equivalence for proportions were made using two-sided confidence intervals (CIs) for the difference in response rate (bid-tid) based on the normal distribution approximation to the binomial distribution. The bid treatment group was considered as effective as the tid group if the lower limit of the 95% confidence interval was not below -10%. It should be noted that the study was not designed to demonstrate non-inferiority for secondary end-points where the numbers of patients was expected to be too small to draw any conclusions.</p>		
<p><b>Study Population:</b> Male and female subjects, aged between 2 and 12 years inclusive, with a clinical diagnosis of recurrent tonsillitis, defined by having three or more episodes of confirmed tonsillitis requiring treatment with antibiotics during the year prior to the screening visit, were eligible for the study. Subjects were also to have a clear diagnosis of tonsillitis. In all cases written informed consent was obtained from a parent or legal guardian. Subjects who received systemic antibiotics within seven days prior to inclusion in the study, or subjects with concomitant infection were excluded.</p>		
	<b>Amoxicillin/clavulanate 30/7.5 mg/kg/day tid</b>	<b>Amoxicillin/clavulanate 35/5 mg/kg/day bid</b>
<b>Number of Subjects:</b>		
Planned, N	215	215
Randomised, N	247	248
Completed, n (%)	220 (89.1)	221 (89.1)
Total Number Subjects Withdrawn, n (%)	27 (10.9)	27 (10.9)
Withdrawn due to Adverse Events, n (%)	5 (2.0)	3 (1.2)
Withdrawn due to Lack of Efficacy, n (%)	2 (0.8)	3 (1.2)
Withdrawn for Other Reasons, n (%)	20 (8.1)	21 (8.5)
	<b>Amoxicillin/clavulanate 30/7.5 mg/kg/day tid</b>	<b>Amoxicillin/clavulanate 35/5 mg/kg/day bid</b>
<b>Demographics</b>		
N (ITT)	247	248
Females: Males	113: 134	127: 121
Mean Age, years (SD)	6.0 (2.6)	5.8 (2.8)
Caucasian, n (%)	245 (99.2)	246 (99.2)
<b>Primary Efficacy Results: (ITT population)</b>		
Clinical response at the end of therapy	<b>Amoxicillin/clavulanate 30/7.5 mg/kg/day tid (N=247)</b>	<b>Amoxicillin/clavulanate 35/5 mg/kg/day bid (N=248)</b>
Success, n (%)	237 (96.0)	241 (97.2)
Failure, n (%)	10 (4.0)	7 (2.8)
Treatment difference (bid vs tid)	1.23	
95% CI	-1.98, 4.43	
p-value	Not applicable	
<b>Secondary Outcome Variable(s): (ITT population)</b>		
	<b>Amoxicillin/clavulanate 30/7.5 mg/kg/day tid (N=247)</b>	<b>Amoxicillin/clavulanate 35/5 mg/kg/day bid (N=248)</b>
Recurrence of tonsillitis at follow-up, N	237	241
Success (persistent cure), n (%)	203 (85.7)	220 (91.3)
Failure (recurrence), n (%)	34 (14.3)	21 (8.7)
Treatment difference (BID vs TID)	5.63	
95% CI	-0.08, 11.34	
<b>GABHs bacteriological response and outcome:</b>		
Response/outcome at end of therapy, N	81	79
Success - proven eradication	68 (84.0)	76 (96.2)
Success - presumed eradication	7 (8.6)	0
Failure - persistence	6 (7.4)	3 (3.8)
Failure - indeterminate	0	0
Response/outcome at follow-up, N	74	76

Success - proven eradication	64 (86.5)	66 (86.8)
Success - presumed eradication	0	0
Failure - persistence	4 (5.4)	1 (1.3)
Failure - eradication with re-infection	4 (5.4)	9 (11.8)
Failure - indeterminate	2 (2.7)	0
Primary pathogens bacteriological response and outcome:		
Response at end of therapy, N	128	126
Success - proven eradication	107 (83.6)	115 (91.3)
Success - presumed eradication	7 (5.5)	2 (1.6)
Failure - persistence	14 (10.9)	9 (7.1)
Failure - indeterminate	0	0
Response at follow-up, N	121	121
Success - proven eradication	96 (79.3)	99 (81.8)
Success - presumed eradication	0	1 (0.8)
Failure - persistence	9 (7.4)	3 (2.5)
Failure - eradication with re-infection	13 (10.7)	18 (14.9)
Failure - indeterminate	3 (2.5)	0
Emergence of new organisms at end of therapy, N	232	240
Superinfection, n (%)	3 (1.3)	2 (0.8)
Colonisation, n (%)	51 (22.0)	43 (17.9)
No new organism, n (%)	178 (76.7)	195 (81.3)
Emergence of new organisms at follow-up, N	232	238
Superinfection, n (%)	7 (3.0)	4 (1.7)
Colonisation, n (%)	36 (15.5)	47 (19.7)
No new organism, n (%)	189 (81.5)	187 (78.6)
Global clinical response rate, %	82.2	88.7
Treatment difference (bid vs tid)	6.52	
95% CI	0.34, 12.71	
Signs and symptoms of tonsillitis: all specific signs and symptoms of tonsillitis were markedly reduced from baseline by the Visit 3 assessment. There were no obvious differences between treatment groups.		
Time to return to normal temperature		
Subjects with fever, N	138	145
Days to temperature normalisation, median (interquartile range)	2 (1-3)	2 (1-3)
<b>Safety Results: ITT Population</b> – Adverse events (AEs) were reported that occurred during the study up to follow-up (Visit 4, Day 35±7). Any serious AEs (SAEs) occurring during the study or within 30 days, of receiving the last dose of study medication, were reported.		
	<b>Amoxicillin/clavulanate 30/7.5 mg/kg/day tid (N=247)</b>	<b>Amoxicillin/clavulanate 35/5 mg/kg/day bid (N=248)</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 (%)	79 (32.0)	75 (30.2)
Coughing	6 (2.4)	14 (5.6)
Vomiting	13 (5.3)	10 (4.0)
Rhinitis	15 (6.1)	9 (3.6)
Bronchitis	13 (5.3)	7 (2.8)
Viral infection	4 (1.6)	7 (2.8)
Abdominal pain	4 (1.6)	6 (2.4)
Ear disorder, not otherwise specified	3 (1.2)	6 (2.4)
Otitis media	10 (4.0)	5 (2.0)
Diarrhoea	7 (2.8)	5 (2.0)
Pharyngitis	7 (2.8)	5 (2.0)
Headache	5 (2.0)	5 (2.0)
Sinusitis	2 (0.8)	5 (2.0)

Eczema	1 (0.4)	5 (2.0)
Fever	8 (3.2)	4 (1.6)
<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 30/7.5 mg/kg/day tid (N=247)</b>	<b>Amoxicillin/clavulanate 35/5 mg/kg/day bid (N=248)</b>
Subjects with non-fatal SAEs, n (%)	3 (1.2)	2 (0.8)
	<b>n (%) [related]</b>	<b>n (%) [related]</b>
Correction of squint	0	1 (0.4) [0]
Vomiting	0	1 (0.4) [0]
Abdominal pain	1 (0.4) [1]	0
Constipation	1 (0.4) [1]	0
Pneumonia	1 (0.4) [0]	0
Urinary tract infection	1 (0.4) [0]	0
Subjects with fatal SAEs, n (%)	0	0
<b>Per Protocol Diarrhea</b>	<b>Amoxicillin/clavulanate 30/7.5 mg/kg/day tid (N=241)</b>	<b>Amoxicillin/clavulanate 35/5 mg/kg/day bid (N=243)</b>
Diarrhea, n (%)	8 (3.3)	8 (3.3)
95% C.I.	-3.21%, 3.16%	

**Conclusion:**

Twice daily (bid) amoxicillin/clavulanate 35/5mg/kg/day was as effective as three times daily (tid) amoxicillin clavulanate 30/7.5mg/kg/day in this study.

In total, 79 subjects (32.0%) and 75 subjects (30.2%) experienced AEs in the amoxicillin/clavulanate tid and amoxicillin/clavulanate bid treatment groups, respectively. The most common AEs were vomiting, rhinitis and bronchitis in the amoxicillin/clavulanate tid treatment group, and coughing, vomiting and rhinitis in the amoxicillin/clavulanate bid treatment group.

Non-fatal SAEs were experienced by three subjects (1.2%) in the amoxicillin/clavulanate tid treatment group and two subjects (0.8%) in the amoxicillin/clavulanate bid treatment group; no SAE was experienced by more than one subject. No fatal SAEs were reported during the course of this study. The incidence of protocol defined diarrhea was very low and similar in both treatment groups.

**Publications:**

No Publication

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