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<b>Study No:</b> 446	
<b>Title:</b> Comparison of Amoxicillin Concentrations in Plasma and Middle Ear Fluid Following Administration of Augmentin 45/3.2 mg/kg to Pediatric Patients with Acute Otitis Media.	
<b>Rationale:</b> Treatment failures in patients with acute otitis media (AOM) have often been related to poor penetration of the antimicrobial agent into the middle ear fluid (MEF) combined with higher minimum inhibitory concentrations of the pathogens, especially resistant <i>pneumococci</i> . There is no single oral antibiotic currently available that can be used initially that will be effective against all of the common pathogens causing AOM, including the resistant <i>pneumococcus</i> . The 14:1 amoxicillin:clavulanate formulation ratio was chosen to attain higher plasma concentrations, and therefore higher MEF concentrations of amoxicillin.	
<b>Phase:</b> I	
<b>Study Period:</b> 29 February 1996 to 03 June 1996.	
<b>Study Design:</b> An open-label, study. Blood and MEF specimen were collected at 1, 2, or 3 hours after dosing based on a randomization schedule for determination of amoxicillin concentrations.	
<b>Centers:</b> One center in the USA.	
<b>Indication:</b> acute otitis media	
<b>Treatment:</b> Subjects were administered amoxicillin:clavulanate 90/6.4 mg/kg/day divided into two equal doses (45/3.2 mg/kg) every 12 hours for 10 days.	
<b>Objectives:</b> To determine the MEF and plasma concentrations of amoxicillin at 1, 2 and 3 hours after administration of a single oral dose of amoxicillin:clavulanate 45/3.2 mg/kg; to evaluate the tolerability of amoxicillin:clavulanate when given in the dose of 45/3.2 mg/kg every twelve hours for ten days.	
<b>Statistical Methods:</b> Pharmacokinetics (PK) were assessed for all subjects who provided blood and MEF samples. Safety was assessed in all subjects who received study medication. Descriptive statistics were calculated for demographic data, as well as for plasma and MEF concentrations of amoxicillin. No formal statistical analysis was performed.	
<b>Study Population:</b> Male or female children, 3 months to 12 years of age (inclusive) with a diagnosis of AOM based on the presence of at least one of the following symptoms/signs: a) acute ear pain within the previous 24 hours. b) marked erythema of the tympanic membrane. c) fullness or bulging of the tympanic membrane. Plus, middle ear effusion evidenced by at least two of the following: a) decreased or absent mobility of the tympanic membrane by pneumatic otoscopy or tympanometry. b) yellow or white discoloration of the tympanic membrane. c) opacification of the tympanic membrane. Subjects with history of allergy to penicillins or intolerance of amoxicillin:clavulanate or who had received any systemic antibiotic in the previous 24 hours were excluded.	
<b>Number of Subjects:</b>	<b>Amoxicillin:clavulanate (90/6.4 mg/kg/day)</b>
Planned N	minimum of 18
Dosed N	19
Completed n (%)	16 (84.2)
Total Number Subjects Withdrawn n (%)	3 (15.8)
Withdrawn due to Adverse Events n (%)	1 (5.3)
Withdrawn due to Lack of Efficacy n (%)	0
Withdrawn for Other Reasons n (%)	2 (10.5)
<b>Demographics</b>	<b>Amoxicillin:clavulanate (90/6.4 mg/kg/day)</b>
N (ITT)	19
Females: Males	7:12
Mean Age in Months (sd)	32 (23.3)
Mean Weight in Kg (sd)	15.0 (5.24)
Black n (%)	11 (57.9)

<b>Pharmacokinetic (PK) Results:</b>			
<b>Time point</b>	<b>Amoxicillin plasma concentration (mcg/mL)</b>	<b>Amoxicillin MEF concentration (mcg/mL)</b>	<b>Amoxicillin MEF/plasma ratio</b>
1 hour			
N	5	4	4
Arithmetic Mean	7.7	3.2	0.32
Median (range)	9.3 (1.5 to 14.0)	3.5 (0.2 to 5.5)	0.30 (0.08 to 0.59)
2 hours			
N	7	5	5
Arithmetic Mean	15.7	3.3	0.21
Median (range)	13.0 (11.0 to 25.0)	2.4 (1.9 to 6.0)	0.20 (0.08 to 0.35)
3 hours			
N	5	5	5
Arithmetic Mean	13.0	5.8	0.53
Median (range)	12.0 (5.5 to 21.0)	6.5 (3.9 to 7.4)	0.62 (0.32 to 0.71)
<b>Safety Results: Safety Population</b> -Any adverse experiences (AEs) that occurred from Day 1 to Day 14 were recorded.			
<b>Adverse Events:</b>		<b>Amoxicillin:clavulanate (90/6.2 mg/kg/day)</b>	
N (ITT)		19	
No. subjects with AEs n (%)		10 (52.6)	
Most Frequent AEs			
Diarrhea		5 (26.3)	
Earache		4 (21.1)	
<b>Serious Adverse Events (SAEs), n (%) [n considered by the investigator to be related]:</b>			
N		19	
No. subjects with SAEs, n (%) [related] -includes fatal and non-fatal events		0	

**Publications:**

Middle ear fluid concentrations of amoxicillin after large dosages in children with acute otitis media. Seikel, K., Shelton, S., and McCracken, G. H. Jr *Pediatr Infect Dis J* 98; 17(10):969-70

Date Updated: 10-Oct-05