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Study No.: 25000/542	
Title: Middle ear fluid penetration of augmentin paediatric formulation (100mg-12.5mg/ml) given as a 80mg-10mg/kg/day dosage regimen divided into three intakes.	
Rationale: The treatment of bacterial acute otitis media (AOM) must take into account the bacteria involved, their current susceptibilities to antimicrobial agents, and the identified therapeutic predictive pharmacodynamic (PD) parameters. The aim of this pharmacokinetic (PK) study was to assess amoxicillin/clavulanate parameters in middle ear fluid (MEF) and to establish its penetration in order to ensure adequacy in otitis treatment.	
Phase: I	
Study Period: 20 September 1995 to 17 May 2001.	
Study Design: Multicentre, open-label study.	
Centres: 7 centres in France.	
Indication: Serous otitis media.	
Treatment: Subjects were randomised into 5 groups all receiving 80/10mg/kg/day amoxicillin/clavulanic acid in 3 doses over 3 days: Group 1: Last intake 1 hour before surgery, Group 2: Last intake 2 hours before surgery, Group 3: Last intake 3 hours before surgery, Group 4: Last intake 8 hours before surgery, Group 5: Last intake 12 hours before surgery.	
Objectives: The objectives were to assess amoxicillin/clavulanate paediatric formulation PK/PD values through the measurement of amoxicillin and clavulanic acid concentrations in blood and MEF in paediatric subjects using this antibiotic.	
Statistical Methods: Summary statistics were provided; no formal analysis was conducted. The PK population included all subjects who had received at least 1 dose of study drug and without major deviation. The safety population included all subjects who had received at least 1 dose of study drug. PK/PD parameters measured in this study included time above the minimum inhibitory concentration (T>MIC), drug concentrations (mg/L) in blood and MEF, and inhibitory quotient (calculated as drug concentration/ MIC).	
Study Population: Subjects aged 12 years or less with a middle ear chronic bilateral discharge and acute superinfection were enrolled if they were to undergo tympanostomy tube surgery. Subjects were excluded if they had received systemic antibiotherapy or drugs that could modify amoxicillin/clavulanate PK (e.g. probenecid) within the previous 8 days.	
Number of Subjects:	Amoxicillin/clavulanate
Planned, N	40
Enrolled, N	59
Dosed, N	56
Completed, n (%)	55 (93)
Total Number Subjects Withdrawn, n (%)	4 (7)
Withdrawn due to Adverse Events, n (%)	0
Withdrawn due to Lack of Efficacy, n (%)	0
Withdrawn for Other Reasons, n (%)	4 (7)
Demographics	
N (PK Population)	36
Females: Males	14: 22
Mean Age in Years (Range)	4.7 (1.3 to 14.4)
Mean Weight in Kg (Range)	17 (10 to 42)
Race, n (%)	n/a
PK and PD Endpoints: (PK Population)	
T>MIC (Time blood concentration >minimum inhibitory concentration), %	

	Delay of 8 hours after last administration (N=6)	Delay of 12 hours after last administration (N=7)			
MIC 0.1 mg/L	100	100			
MIC 0.5 mg/L	100	100			
MIC 1 mg/L	100	66			
MIC 2 mg/L	87.5	58			
T>MIC (Time MEF concentration >minimum inhibitory concentration), %:					
100% with a delay of 12 hours after last administration (N=7) for MICs 0.1 to 2 mg/L					
Middle Ear Fluid Concentration, mg/L					
	Group 1 (N=8)	Group 2 (N=7)	Group 3 (N=8)	Group 4 (N=6)	Group 5 (N=7)
Amoxicillin	7.23	7.4	7.08	6.01	3.31
Clavulanic acid	0.58	0.94	0.62	0.11	0.11
Amoxicillin inhibitory quotient in middle ear fluid					
	Group 1 (N=8)	Group 2 (N=7)	Group 3 (N=8)	Group 4 (N=6)	Group 5 (N=7)
MIC 0.1 mg/L	72	74	71	60	33
MIC 0.5 mg/L	14.5	15	14	12	6.5
MIC 1 mg/L	7	7.5	7	6	3
MIC 2 mg/L	3.5	3.7	3.5	3	1.5
Safety Results: (Safety Population) - An on-therapy adverse event (AE) was defined as an AE with onset on or after the start date of study medication but not later than one day after the last date of study medication. An on-therapy serious adverse event (SAE) was defined as a SAE with onset on or after the start date of study medication and up to 30 days after the last dose of medication.					
Adverse Events:			Amoxicillin/clavulanate		
N (Safety)			56		
Subjects with any AE(s), n (%)			5 (9)		
Diarrhoea			2 (3)		
Post-operative complications			2 (3)		
Gastrointestinal disorders			1 (2)		
Serious Adverse Events, n (%) [# considered by the investigator to be related, possibly related, or probably related to study medication]:					
Subjects with non-fatal SAE(s), n (%)			0		
Subjects with fatal SAE(s), n (%)			0		

Publications:
Jehl-F;Bobin-S;Schatz-P;Balouka-JB;Rohmar-D;Wagner-B;Woerther-JP;Roger-G;Dubreuil-C;Klossek-JM;Romanet-D;Triglia-JM;Renault-C;Borie-C;Rouffiac-E **Middle ear fluid penetration of Augmentin pediatric formulation (100 mg-12.5 mg/ml) at dosage of 80 mg -10 mg kg (-1) d(-1), 3 times a day;Pénétration intra-auriculaire d'Augmentin Forme pédiatrique per os (100 mg-12,5 mg/ml d'amoxicilline/acide clavulanique) administrée à la posologie de 80 mg-10 mg kg (-1) j(-1) en 3 prises.** MEDECINE ET MALADIES INFECTIEUSES 2003; 33(3):155-160.

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