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Study No.: 382				
Title: A parallel group study to estimate the steady state pharmacokinetics of amoxicillin and clavulanate in paediatric patients in the age range 1 month to 12 years administered <i>Augmentin</i> ® 45/6.4 mg/kg/day (twice daily) or 40/10 mg/kg/day (three times daily) orally.				
Rationale: Previous studies in adults have demonstrated that a new dosing regimen of amoxicillin/clavulanate (AM/CL) 875/125 mg twice daily (bid) produces comparable efficacy and plasma concentrations of AM to the standard regimen of AM/CL 500/125 mg three times a day (tid). This study was designed to assess the steady state pharmacokinetics in children (aged 1 month to 12 years) employing both the conventional paediatric tid dosing regimen (40/10 mg/kg/day) and the proposed bid dosing regimen with a modified AM/CL ratio of 7:1 (45/6.4 mg/kg/day).				
Phase: I				
Study Period: 19 September 1994 to 9 February 1995.				
Study Design: An open-label, parallel-group, randomised study.				
Centres: 3 centres in the United Kingdom and 1 in the United States.				
Indication: Infection requiring treatment with an oral antibiotic				
Treatment: Oral AM/CL was administered in a fixed dose regimen either 8 hourly (tid) or 12 hourly (bid) for up to 10 days; the doses to be administered were as follows: AM/CL 45/6.4 mg/kg/day bid and AM/CL 40/10 mg/kg/day tid. Where possible, dosing was given immediately before a meal and at least 3 hours after the previous meal.				
Objectives: The primary objectives were to establish the steady state pharmacokinetic profiles of AM and CL in children of various ages (1 month to 12 years); to evaluate the steady state pharmacokinetic profiles of AM and CL after giving AM/CL 45/6.4 mg/kg/day bid or AM/CL 40/10 mg/kg/day tid.				
Primary Outcome/Efficacy Variable: The primary outcome variables were maximum observed plasma concentration (C_{max}), time to reach C_{max} (T_{max}), apparent terminal elimination half-life ($T_{1/2}$), area under the plasma concentration-time curve from time zero to the last quantifiable plasma concentration ($AUC_{(0-t)}$) and time above the minimum inhibitory plasma concentration (TMIC) for AM and CL.				
Secondary Outcome/Efficacy Variable(s): No secondary outcome variables were included in this study.				
Statistical Methods: Descriptive statistics were calculated by age group and dosing regimen for all pharmacokinetic parameters. Clinical monitoring and laboratory data were reviewed by the study physician but were not formally analysed. All subjects who received at least 1 dose of study medication were included in the safety population; subjects were included in the evaluable population if a full pharmacokinetic profile was obtained prior to withdrawal.				
Study Population: Male and female subjects, aged 1 month to 12 years, who were suffering from an infection, requiring treatment with an oral antibiotic at the specified doses in the protocol, which was not considered to affect renal function, were eligible for inclusion in the study. Subjects were not to have any clinical evidence of renal disease or kidney infection.				
Number of Subjects	AM/CL tid		AM/CL bid	
Planned, N	15		15	
Randomised, N	6		5	
Completed, n (%)	5 (83)		5 (100)	
Total Number Subjects Withdrawn, n (%)	1 (17)		0	
Withdrawn due to Adverse Events, n (%)	1 (17)		0	
Withdrawn due to Lack of Efficacy, n (%)	0		0	
Withdrawn for other reasons, n (%)	0		0	
Demographics	Subjects aged 2 to 12 years		Subjects aged under 1 year	
	AM/CL tid	AM/CL bid	AM/CL tid	AM/CL bid
N (safety population)	4	4	2	1
Females: Males	3: 1	3: 1	1: 1	0: 1
Mean Age, years (range)	6 (2 – 9)	8 (6 – 12)	5 (1 – 9) ^a	4 (NA) ^a
White, n (%)	4 (100)	4 (100)	2 (100)	1 (100)

NA: not applicable. Age information provided in months.				
Primary Results	Subjects aged 2 to 12 years		Subjects aged under 1 year	
	AM/CL tid (n = 4)	AM/CL bid (n = 4)	AM/CL tid (n = 2)	AM/CL bid (n = 1)
Pharmacokinetic parameters for AM (evaluable population)				
C _{max} (µg/mL), mean (range)	7.33 (4.97-9.07)	11.99 (8.25-15.29)	3.51 (3.16-3.86)	6.61 (NA)
AUC _(0-t) (µg.h/mL), mean (range)	18.6 (16.4-21.7)	35.2 (30.6-42.2)	17.4 (10.7-24.0) ^b	23.7 (NA)
T _{max} (h), median (range)	2.1 (1.2-3.0)	1.0 (1.0-2.0)	3.0 (2.0-3.9)	3.1 (NA)
T _{1/2} (h), mean (range)	1.02 (0.62-1.42)	1.22 (0.90-1.46)	3.19 (1.26-5.12)	1.19 (NA)
TMIC (h), mean (range)	4.68 (3.83-5.44)	6.15 (4.89-6.86)	6.53 (5.06-8.00)	5.72 (NA)
Predicted TMIC over 24h (h), mean	14.04	12.30	19.6	11.44
Pharmacokinetic parameters for CL (evaluable population)				
C _{max} (µg/mL), mean (range)	2.66 (0.93-4.77)	5.49 (1.97-8.58)	0.53 (0.13-0.93)	0.54 (NA)
AUC _(0-t) (µg.h/mL), mean (range)	5.51 (1.48-8.92)	13.26 (4.71-17.68)	2.12 (0.49-3.75)	1.26 (NA)
T _{max} (h), median (range)	1.6 (1.0-2.0)	1.0 (1.0-2.0)	2.0 (2.0-2.0)	2.0 (NA)
T _{1/2} (h), mean (range)	0.94 (0.88-0.99)	0.99 (0.85-1.18)	1.61 (1.35-1.86)	0.98 (NA)
TMIC (h), mean (range)	3.27 (1.94-3.88)	4.90 (3.37-6.33)	1.71 (0.00-3.42)	0.30 (NA)
Predicted TMIC over 24h (h), mean	9.81	9.80	5.13	0.60
NA: not applicable. AUC ₍₀₋₈₎ rather than AUC _(0-t) presented here.				
Secondary Outcome Variable(s): No secondary outcome variables recorded.				
Safety Results: Safety Population - On therapy adverse events (AEs) were defined as any event occurring after the start of the study (once informed consent was obtained) until follow-up. All serious AEs (SAEs) occurring during the clinical trial or within 30 days of receiving the last dose of study drug were to be reported. Subjects with AEs were to be followed-up until the event had subsided or the condition had stabilised.				
Adverse Events – On-Therapy	AM/CL tid		AM/CL bid	
N	6		5	
No. subjects with AE(s), n (%)	1 (17)		2 (40)	
Serious Adverse Events – On-Therapy plus 30 Days Post-Therapy n (%), [n considered by the investigator to be related to study medication]				
	AM/CL tid		AM/CL bid	
N	6		5	
No. subjects with SAEs, n (%) [related]	0		0	

Publications:
No Publication

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