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<b>Study No.:</b> 233
<b>Title:</b> A Comparison of the Efficacy and Safety of Augmentin 875/125 mg po q 12 hrs and Augmentin 500/125 mg po q 8 hrs in the Treatment of Pyelonephritis and Complicated Urinary Tract Infections. A Double-Blind, Multi-Center, Comparative Study.
<b>Rationale:</b> At the time of the study, amoxicillin/clavulanate was dosed at 500/125 mg orally (po) every (q) 8 hours (three times a day, tid) for the treatment of pyelonephritis and complicated urinary tract infections (UTIs). This study was to determine if the administration of amoxicillin/clavulanate 875/125 mg po every 12 hours (twice daily, bid) was no more than 15% better or worse than the existing dosing regimen for the treatment of these infections. The proposed change in dosage was supported by pharmacokinetic, microbiological and <i>in vivo</i> animal data.
<b>Phase:</b> III
<b>Study Period:</b> 24 July 1992 to 31 August 1993.
<b>Study Design:</b> A randomized, double-blind, double-dummy, multicenter comparative study. Subjects enrolled in the original and modified protocols (24Feb92, 24Jul92 and 23Feb93) were instructed to attend the clinic for a preliminary visit (Day -1 to 0), on-therapy visit (Day 2-4), end of therapy visit (48-96 hours post-therapy) and follow up visit (2-4 weeks post-therapy). Subjects enrolled in the amended protocol (14Apr93) were instructed to attend the clinic for a preliminary visit (Day -1 to 0), on-therapy visit (Day 2-4), end of therapy visit (5-9 days post-therapy), follow up visit 1 (2-4 weeks post-therapy) and follow up visit 2 (4-6 weeks post-therapy). Subjects enrolled in the original and modified protocols (24Feb92, 24Jul92 and 23Feb93) were assigned patient identification numbers (PIDs) <80,000. Subjects enrolled in the amended protocol (14Apr93) were assigned patient identification numbers (PIDs) ≥80,000.
<b>Centers:</b> 46 centers in United States.
<b>Indication:</b> Pyelonephritis and complicated UTIs.
<b>Treatment:</b> Subjects were randomized to one of two treatments in a 1:1 ratio for 7 to 14 days: amoxicillin/clavulanate 875/125 mg po every 12 hours (plus placebo amoxicillin/clavulanate 500/125 mg po every 8 hours), or amoxicillin/clavulanate 500/125 mg po every 8 hours (plus placebo amoxicillin/clavulanate 875/125 mg po every 12 hours).
<b>Objectives:</b> The objective was to compare the efficacy and safety of amoxicillin/clavulanate 875/125 mg po every 12 hours and amoxicillin/clavulanate 500/125 mg po every 8 hours in the treatment of subjects with pyelonephritis and complicated UTIs.
<b>Primary Outcome/Efficacy Variable:</b> Clinical and bacteriological responses (success or failure) at first follow-up (2 to 4 weeks post-therapy). Clinical success at follow up was defined as sufficient resolution of pyelonephritis or UTI such that no additional antibacterial therapy for pyelonephritis or UTI was indicated. Clinical failure at follow up was defined as reappearance or deterioration of pyelonephritis or UTI following clinical success at end of therapy. If a patient was deemed to be a clinical failure at any stage, this outcome was carried forward to all further visits. Bacteriological success was defined as the eradication or, in the absence of an evaluable repeat culture sample, clinical evidence of eradication of all initial screening pathogens without superinfection or new infection. Bacteriological failure was defined as the persistence or recurrence of an initial screening pathogen, or the presence of a new pathogen in a repeat culture sample. For subjects with no repeat culture sample available, bacteriological failure was presumed if clinical signs and symptoms persisted to a degree that necessitated further antibacterial therapy for the indication under investigation. If a subject was deemed to be a bacteriological failure at any stage, this outcome was carried forward to all further visits.
<b>Secondary Outcome/Efficacy Variable(s):</b> Clinical and bacteriological responses (success or failure) at end of therapy. Clinical success at end of therapy was defined as sufficient resolution of pyelonephritis or UTI such that no additional antibacterial therapy for pyelonephritis or UTI was indicated. Clinical failure was recorded when there was insufficient improvement of pyelonephritis or UTI at end of therapy requiring additional antibacterial therapy.
Clinical and bacteriological responses (success or failure) at the second follow-up visit.
<b>Statistical Methods:</b> The Clinical intent-to-treat (ITT) population included all subjects who received study treatment, had a clinical diagnosis of pyelonephritis or a complicated UTI and had clinical assessments at both pre-therapy and post-therapy visits. The Clinical Per-Protocol (PP) population was a subset of the ITT population without specific pre-defined protocol violations. The Bacteriological PP population included all subjects who received study treatment, had a clinical diagnosis of pyelonephritis or a complicated UTI, had bacteriological assessments at both pre-therapy and post-therapy visits and a pre-therapy urine culture containing ≥10 <sup>5</sup> colony forming units (CFU)/mL of a

uropathogen obtained not more than two days prior to, but not after, study medication start, and were without specific pre-defined protocol violations. The PP population was the primary population for evaluation of efficacy. Safety was evaluated in all patients who were randomized.

The equivalence of the two treatment groups was evaluated using two-sided 95% confidence intervals (CIs) for the difference (q 12 – q 8) in the proportion of patients who were bacteriological or clinical success. The twice daily group was considered at least as equivalent as the three times daily group if the lower limit of the CI was not less than -15%. It should be noted that the study was not designed to demonstrate equivalence for secondary end-points where the numbers of patients was too small to draw any conclusions.

**Study Population:** Subjects aged 12 years or older and diagnosed with either pyelonephritis (defined as fever and/or flank pain or costovertebral angle tenderness) or a complicated UTI (defined as dysuria, frequency and/or urgency AND a neurological or anatomical abnormality fitting into one of the following categories: prostatic obstruction, neurogenic bladder, urethral stricture, calculi, or other), with a microscopic examination and/or Gram's stain of clean-voided mid-stream urine or catheter urine consistent with a bacterial UTI. Subjects with vaginitis, genital herpes or an uncomplicated UTI, subjects with an indwelling Foley catheter, and subjects who had received antibiotic therapy within two weeks prior to the initiation of the study were excluded.

	<b>Amoxicillin/clavulanate 500/125 q 8 hours</b>	<b>Amoxicillin/clavulanate 875/125 q 12 hours</b>
Number of Subjects:		
Planned (at the first follow-up visit), N	115	115
Randomized, N	323	311
Clinical PP population at first follow-up, N	98	99
Bacteriological PP population at first follow-up, N	97	86
Completed, n (%)	205 (63.5)	217 (69.8)
Total Number Subjects Withdrawn, n (%)	118 (36.5)	94 (30.2)
Withdrawn due to Adverse Events, n (%)	30 (9.3)	15 (4.8)
Withdrawn due to Lack of Efficacy, n (%)	4 (1.2)	4 (1.3)
Withdrawn for Other Reasons, n (%)	84 (26.0)	75 (24.1)
<b>Demographics</b>	<b>Amoxicillin/clavulanate 500/125 q 8 hours</b>	<b>Amoxicillin/clavulanate 875/125 q 12 hours</b>
N (ITT)	321	308
Females: Males	256: 65	248: 60
Mean Age, years (SD)	48.8 (22.4)	49.5 (21.7)
White, n (%)	245 (76.3)	244 (79.2)
<b>Primary Efficacy Results:</b>		
	<b>Amoxicillin/clavulanate 500/125 q 8 hours</b>	<b>Amoxicillin/clavulanate 875/125 q 12 hours</b>
Clinical response at first follow-up (2 to 4 weeks post-therapy): (Clinical PP Population who were successes at end of therapy)		
Success, all infections, n/N (%)	73/98 (74.5)	75/99 (75.8)
Treatment difference, 95% CI	-10.8, 13.3	
p-value	Not available	
Success, pyelonephritis, n/N (%)	42/56 (75.0)	48/62 (77.4)
Treatment difference, 95% CI	-13.0, 17.8	
p-value	Not available	
Success, complicated UTI, n/N (%)	31/42 (73.8)	27/37 (73.0)
Treatment difference, 95% CI	-20.4, 18.7	
p-value	Not available	
Bacteriological response at first follow-up (2 to 4 weeks post-therapy): (Bacteriological PP Population who were successes at end of therapy)		
Success, all infections, n/N (%)	49/97 (50.5)	50/86 (58.1)
Treatment difference, 95% CI	-6.8, 22.0	
p-value	0.159	
Success, pyelonephritis, n/N (%)	33/54 (61.1)	32/52 (61.5)
Treatment difference, 95% CI	-18.1, 19.0	
p-value	Not available	
Success, complicated UTI, n/N (%)	16/43 (37.2)	18/34 (52.9)

Treatment difference, 95% CI	-6.4, 37.9	
p-value	Not available	
<b>Secondary Outcome Variable(s):</b>		
	<b>Amoxicillin/clavulanate 500/125 q 8 hours</b>	<b>Amoxicillin/clavulanate 875/125 q 12 hours</b>
Clinical response at end of therapy (48 to 96 hours post-therapy): (Clinical PP Population, PIDs <80,000)		
Success, all infections, n/N (%)	55/57 (96.5)	66/69 (95.7)
Treatment difference, 95% CI	-7.6, 5.9	
Success, pyelonephritis, n/N (%)	33/34 (97.1)	43/44 (97.7)
Treatment difference, 95% CI	-6.5, 7.9	
Success, complicated UTI, n/N (%)	22/23 (95.7)	23/25 (92.0)
Treatment difference, 95% CI	-17.2, 9.9	
Clinical response at end of therapy (5 to 9 days post-therapy): (Clinical PP Population, PIDs ≥80,000)		
Success, all infections, n/N (%)	49/56 (87.6)	45/50 (90.0)
Treatment difference, 95% CI	-9.5, 14.5	
Success, pyelonephritis, n/N (%)	29/32 (90.6)	23/27 (85.2)
Treatment difference, 95% CI	-22.2, 11.3	
Success, complicated UTI, n/N (%)	20/24 (83.4)	22/23 (95.8)
Treatment difference, 95% CI	-4.8, 29.4	
Bacteriological response at end of therapy (48 to 96 hours post -therapy): (Bacteriological PP Population, PIDs <80,000)		
Success, all infections, n/N (%)	43/54 (79.6)	47/58 (81.0)
Treatment difference, 95% CI	-13.3, 16.1	
Success, pyelonephritis, n/N (%)	26/33 (78.8)	30/36 (83.3)
Treatment difference, 95% CI	-14.0, 23.1	
Success, complicated UTI, n/N (%)	17/21 (81.0)	17/22 (77.3)
Treatment difference, 95% CI	-27.9, 20.6	
Bacteriological response at end of therapy (5 to 9 days post -therapy): (Bacteriological PP Population, PIDs ≥80,000)		
Success, all infections, n/N (%)	30/54 (55.6)	35/42 (83.3)
Treatment difference, 95% CI	10.4, 45.2	
Success, pyelonephritis, n/N (%)	20/29 (69.0)	18/22 (81.8)
Treatment difference, 95% CI	-10.5, 36.2	
Success, complicated UTI, n/N (%)	10/25 (40.0)	17/20 (85.0)
Treatment difference, 95% CI	20.2, 69.8	
Clinical response at second follow-up (4 to 6 weeks post-therapy): (Clinical PP Population who were previous successes, PIDs ≥80,000)		
Success, all infections, n/N (%)	26/43 (60.5)	18/31 (58.1)
Treatment difference, 95% CI	-25.1, 20.3	
Success, pyelonephritis, n/N (%)	16/24 (66.7)	9/18 (50.0)
Treatment difference, 95% CI	-46.5, 13.2	
Success, complicated UTI, n/N (%)	10/19 (52.6)	9/13 (69.2)
Treatment difference, 95% CI	-17.1, 50.3	
Bacteriological response at second follow-up (4 to 6 weeks post-therapy): (Bacteriological PP Population who were previous successes, PIDs ≥80,000)		
Success, all infections, n/N (%)	15/46 (32.6)	13/29 (44.8)
Treatment difference, 95% CI	-10.4, 34.8	
Success, pyelonephritis, n/N (%)	11/24 (45.8)	7/17 (41.2)
Treatment difference, 95% CI	-35.4, 26.1	
Success, complicated UTI, n/N (%)	4/22 (18.2)	6/12 (50.0)
Treatment difference, 95% CI	-0.7, 64.4	
<b>Safety Results (All Randomized):</b> Adverse events (AEs) were recorded at each study visit from the first on-therapy visit (2 to 4 days) until the last follow-up (2 to 4 weeks for PIDs <80,000; 4 to 6 weeks for PIDs ≥80,000). Adverse Events (AEs) were to be reported on-therapy and through 30 days post-therapy. However, 30 of the AEs listed occurred greater than 30 days post-therapy.		

	<b>Amoxicillin/clavulanate 500/125 q 8 hours (N=323)</b>	<b>Amoxicillin/clavulanate 875/125 q 12 hours (N=311)</b>
<b>Most Frequent Adverse Events – On-Therapy until Follow-up</b>	<b>n (%)</b>	<b>n (%)</b>
Subjects with any AE(s), n (%)	186 (57.6)	174 (55.9)
Diarrhea	53 (16.4)	58 (18.6)
Nausea	29 (9.0)	30 (9.6)
Headache	25 (7.7)	27 (8.7)
Moniliasis genital	18 (5.6)	18 (5.8)
Vomiting	16 (5.0)	15 (4.8)
Abdominal pain	12 (3.7)	14 (4.5)
Vaginitis	11 (3.4)	11 (3.5)
Back pain	4 (1.2)	11 (3.5)
Infection fungal	7 (2.2)	9 (2.9)
Dizziness	6 (1.9)	8 (2.6)
Pruritus genital	9 (2.8)	7 (2.3)
Upper respiratory tract infection	7 (2.2)	1 (0.3)
<b>Serious Adverse Events (SAEs) - On-Therapy until Follow-up</b>		
<b>n (%) [n considered by the investigator to be related to study medication]</b>		
SAEs were to be reported on-therapy and through 30 days post-therapy. However, four of the SAEs listed occurred greater than 30 days post-therapy.		
	<b>Amoxicillin/clavulanate 500/125 q 8 hours (N=323)</b>	<b>Amoxicillin/clavulanate 875/125 q 12 hours (N=311)</b>
Subjects with fatal and non-fatal SAEs, n (%)	20 (6.2)	12 (3.9)
	<b>n (%) [related]</b>	<b>n (%) [related]</b>
Abortion	0	1 (0.3) [0]
Abscess	0	1 (0.3) [0]
Allergic reaction	1 (0.3) [0]	0
Anemia	0	1 (0.3) [0]
Arthritis	1 (0.3) [0]	0
Ascites	1 (0.3) [0]	0
Asthenia	1 (0.3) [0]	0
Back pain	0	1 (0.3) [0]
Bladder calculus	0	1 (0.3) [0]
Bladder carcinoma	0	1 (0.3) [0]
Cataract	1 (0.3) [0]	0
Carcinoma	0	1 (0.3) [0]
Cardiac failure	1 (0.3) [0]	1 (0.3) [0]
Cerebrovascular disorder	1 (0.3) [0]	0
Cholelithiasis	1 (0.3) [0]	0
Colon carcinoma	0	1 (0.3) [0]
Confusion	1 (0.3) [0]	0
Convulsions	0	1 (0.3) [0]
Cyclothymic reaction	1 (0.3) [0]	0
Death fetal	1 (0.3) [0]	0
Dehydration	2 (0.6) [0]	0
Delirium	1 (0.3) [0]	0
Dyspepsia	0	1 (0.3) [1]
Dyspnea	1 (0.3) [0]	0
Dysuria	0	1 (0.3) [0]
Encephalopathy	1 (0.3) [0]	0
Fever	1 (0.3) [0]	0
Gastrointestinal hemorrhage	1 (0.3) [0]	0

Heart disorder	1 (0.3) [0]	0
Injury	1 (0.3) [0]	0
Intestinal obstruction	1 (0.3) [0]	0
Neoplasm, not otherwise specified	1 (0.3) [0]	0
Pneumonia	1 (0.3) [0]	1 (0.3) [0]
Pregnancy unintended	2 (0.6) [0]	1 (0.3) [0]
Pyelonephritis	1 (0.3) [0]	3 (1.0) [0]
Renal calculus	1 (0.3) [0]	0
Renal failure acute	1 (0.3) [0]	1 (0.3) [0]
Renal function abnormal	1 (0.3) [0]	0
Respiratory insufficiency	0	1 (0.3) [0]
Sweating increased	1 (0.3) [0]	0
Tachycardia	1 (0.3) [0]	0
Urinary tract infection	1 (0.3) [1]	0
Vomiting	1 (0.3) [1]	1 (0.3) [1]
Subjects with fatal SAEs, n (%)	3 (0.9)	2 (0.6)
	<b>n (%) [related]</b>	<b>n (%) [related]</b>
Cardiac failure*	0	1 (0.3) [0]
Cerebrovascular disorder	1 (0.3) [0]	0
Heart disorder	1 (0.3) [0]	0
Renal failure acute*	1 (0.3) [0]	1 (0.3) [0]
Respiratory insufficiency*	0	1 (0.3) [0]
*Occurred greater than 30 days post-therapy		

**Conclusion:**

Amoxicillin/clavulanate 875/125mg every 12 hours was both bacteriologically and clinically as efficacious as amoxicillin/clavulanate 500/125 every 8 hours at 2 to 4 weeks post-therapy in treatment of subjects with pyelonephritis and complicated UTIs. Adverse events were reported by 186 (57.6%) subjects in the amoxicillin/clavulanate 500/125 q 8 hours group and by 174 (55.9%) subjects in the amoxicillin/clavulanate 875/125 q 12 hours group, with diarrhea, nausea, and headache being the most frequently reported events in both groups. Serious adverse events were reported in 20 (6.2%) of the subjects in the amoxicillin/clavulanate 500/125 q 8 hours group and by 12 (3.9%) subjects in the amoxicillin/clavulanate 875/125 q 12 hours group. Dehydration and unintended pregnancy were reported in 2 subjects each in the amoxicillin/clavulanate 500/125 q 8 hours group, and pyelonephritis was reported by 3 subjects in the amoxicillin/clavulanate 875/125 q 12 hours group. Two deaths were reported in the amoxicillin/clavulanate 500/125 q 8 hours group.

**Publications:**

No Publication

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