AN EVALUATION OF THE PHARMACOKINETIC, SAFETY AND EFFICACY OF TICARCILLIN/CLAVULANIC ACID IN THE TREATMENT OF BACTERIAL INFECTIONS IN HOSPITALIZED ELDERLY SUBJECTS

by

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A project submitted to the faculty of the
University of Utah in partial fulfillment of the requirements
for the degree of

Doctor of Pharmacy

College of Pharmacy

University of Utah

June 1986

UNIVERSITY OF UTAH COLLEGE OF PHARMACY

FINAL READING APPROVAL

TO THE DOCTOR OF PHARMACY COMMITTEE OF THE UNIVERSITY OF UTAH COLLEGE OF PHARMACY:

I have read the clinical research project report of Charlotte Roost, OSF in its final form and have found that 1) its format, citations, and bibliographic style are consistent and acceptable; 2) its illustrative materials including figures, tables, and charts are in place; and 3) the final manuscript is satisfactory to the Supervisory Committee and is ready for submission to the Doctor of Pharmacy Committee.

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UNIVERSITY OF UTAH COLLEGE OF PHARMACY

SUPERVISORY COMMITTEE APPROVAL

of a clinical research project report submitted by

Charlotte Roost, OSF

We, the undersigned, have read this clinical research project report and have found it to be of satisfactory quality for a Doctor of Pharmacy Degree.

6-18-86
Date

Chairman, Supervisory Committee

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ACKNOWLEDGEMENT

I wish to express my sincere appreciation to the Sisters of St. Francis of Assisi who have given me the opportunity and support to continue my education. I would especially like to acknowledge the retired sisters who have instilled in me an appreciation for the art of aging. Without their prayers and support this would not have been worthwhile.

A special thank you goes to my research committee, Dr. Martin Higbee, Dr. John Bosso and Dr. Manford Gooch for all their guidance, support and friendship. I could not have done it without them.

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INTRODUCTION

The geriatric population has an increased incidence of infections, which results in appreciable morbidity and mortality.[1,2] Alterations in host defense mechanisms with aging contribute to the increased risk of infection.[3] In addition to age related changes in host defenses, such as those of the skin and mucous membranes, there are alterations in the immune system. These changes include alterations in T-lymphocyte subset ratios, with less helper T-cells, which can lead to a decrease in cellular immunity as demonstrated by a lack of response to delayed skin test.[4,5] Chronic, debilitating diseases or conditions such as diabetes mellitus, malignancy, vascular disease or malnutrition, which are more common in the elderly, may increase their susceptibility to infection.[6,7]

Along with the changes in susceptibility to infections, the elderly population has alterations in body composition and physiologic function which may affect the drug disposition of the medications used in the treatment of infections. Changes in drug disposition due to the aging process may lead to changes in the serum drug concentrations (SDC) of antibiotics in the elderly population. This may be reflected as decreased efficacy if the peak SDC is decreased below the minimal inhibitory concentration (MIC) for a specific organism, or increased risk of adverse reactions when the SDC is increased in this population. The pharmacokinetic parameters of drug therapy which are considered to be trends in the elderly population include changes in the volume of distribution due to changes in body composition and excretion, especially renal excretion.[8] Changes in renal function seen in the aged population

are due to a decrease in blood flow to the kidneys, with a decrease in glomerular and tubular function which will decrease the elimination of renally excreted drugs. These possible changes in the disposition of drugs may require an adjustment in the dosages of renally excreted drugs in elderly people. Many of the antibiotics used in the treatment of infections, including the penicillins, are renally excreted.

Ticarcillin/clavulanic acid (Timentin®, Beecham Laboratories, Bristol, TN) has been used for the treatment of a variety of bacterial infections. Ticarcillin (α-carboxyl-3-thienylmethyl penicillin) is a β-lactam antibiotic used in the treatment of infections caused by many gram postive and gram negative bacteria. The β-lactam structure makes the ticarcillin molecule susceptible to degradation by β-lactamase enzymes. Clavulanic acid, an isolate from Streptomycin clavuligerus, irreversibly binds to the β-lactamases of Richmond types II, III, IV and V, thus decreasing the degradation of the ticarcillin by the organisms which produce these types of β-lactamases.[9] The addition of clavulanic acid increases the spectrum of activity of the β-lactam antibiotic active against those organisms which develop resistance through these specific types of β-lactamases.

OBJECTIVE

The objective of this study was to evaluate the pharmacokinetics of the combination of ticarcillin/clavulanic acid in the treatment of bacterial infections in hospitalized elderly subjects. Data regarding the safety and efficacy of ticarcillin/clavulanic acid were also collected.

METHODS

Fifteen (15) male subjects over the age of 62 years were enrolled in this study. The subjects, hospitalized in the Veteran's Administration Medical Center at Salt Lake City, Utah, had a clinical diagnosis of infection either bacteriologically confirmed or suspected of being caused by a microorganism typically susceptible to ticarcillin/clavulanic acid at clinically achievable concentrations. Each subject was enrolled following consultation with their primary physician and the granting of informed consent by the subject, or their legal guardian if the subject was unable to assume responsibility for himself. (See Appendix 1; Informed Consent Form.) Subjects were excluded from the study if they had a history of sensitivity to penicillins or cephalosporins, a serum creatinine greater than 2.5 mg/dL or a calculated or measured creatinine clearance less than 10 mL/min, known severe irreversible liver disease, or if they were also receiving other systemic or topical antibacterial agents from the time of pretreatment cultures until the post-treatment evaluation was completed, or if their medical conditions were such that completion of a five day course of treatment was deemed unlikely by their physicians.

The pretreatment evaluation included the meeting of the inclusion criteria and initial screening which had to be completed within 72 hours prior to the initial administration of the study drug. The screening included a medical history (with an emphasis upon the development of the present infection and the diseases which might affect host resistance to infection) and a detailed drug history. A completed physical examination was performed by the subject's primary

physician or housestaff officer including a detailed description of signs of infection such as fever, vital signs and a description of lesions. A completed blood count (CBC) with white blood cell differential, platelet count, total protein, albumin, total bilirubin, alkaline phosphatase, blood urea nitrogen (BUN), serum creatinine, alanine transaminase (ALT) and/or aspartate transaminase (AST), and serum sodium and potassium were obtained. A clean catch urine sample for routine urinalysis including microscopic examination was also obtained.

Appropriate bacteriological specimens were cultured within 72 hours prior to the initiation of therapy with ticarcillin/clavulanic acid. The infectious organisms were identified and in vitro susceptibilities to ticarcillin and ticarcillin/clavulanic acid were completed by agar disc diffusion technique of susceptibility testing (Kirby-Bauer method) using ticarcillin disks and Timentin® disks containing 75 mcg of ticarcillin plus 20 mcg of clavulanic acid. In order not to deny appropriate antibacterial therapy in cases of suspected infection, ticarcillin/clavulanic acid therapy was begun prior to microbiological confirmation of infection. Radiologic assessment of the evolution of the infectious process was performed when such assessment was indicated in the opinion of one of the investigators in consultation with the primary physician. Diagnosis of the infection was made according to the presenting signs and symptoms and positive specimen cultures, when available. The diagnostic criteria for this study are defined in Appendix 2.

Ticarcillin/clavulanic acid was provided by Beecham Laboratories (lot number BM2868) as vials for reconstitution containing 3 grams of

sterile disodium ticarcillin plus 0.1 gram clavulanic acid as the potassium salt. Inventory control and dispensing of the medication was the responsibility of the hospital's pharmacy department.

Subjects received ticarcillin 3 grams plus clavulanic acid 100 mg diluted with 20 mL sterile water (Abbott #0074-4887-20, lot #82-362-DK), then further diluted in 50 mL 5% dextrose in water (Travenol #2B0081, lot #32V099WS). This solution was infused over 30 minutes through an intravenous catheter (Pre Vue, 20 gauge, #8120), placed into a peripheral vein. The dose was repeated every four to six hours depending on the severity of the infections. The dosing regimen was altered in those subjects with renal impairment (Table 1). The dosing regimen was determined by the principal investigators and the subject's primary physician.

After the initial dose of ticarcillin/clavulanic acid was infused, blood samples were collected for pharmacokinetic evaluation. Three (3) mL samples of blood were obtained from the opposite extremity, through an indwelling venous catheter (Pre Vue, 20 gauge, #8120) with syringes (Monojet 3 mL with 20 gauge, 1 inch needles, #8881). Since the collection was from a heparinized catheter, 3 mL of blood was withdrawn and discarded before sample collection. The collection occurred immediately prior to administration of drug and at 5, 15, 30, 60, 90, 120, 240 and 360 minutes (360 minutes if patients received the study drug every six hours), following completion of a 30 minute infusion. Trough specimens were collected at either 240 or 360 minutes following the 8th or 12th dose and the 16th or 24th dose, depending on the patient's dosing regimen (after 48 and 96 hours of therapy). These trough SDC were evaluated for possible accumulation of the study drug in these elderly subjects.

The blood was transferred to Becton Dickinson tubes without additives (#6490-5J033) and centrifuged in a Damon/IEC, Whisperfuge™ Centrifuge, model #1385, for five minutes at "high speed". The serum was separated and frozen immediately. Samples were stored at minus 70 degrees centigrade for a maximum of 14 days, until analyzed by reverse-phase high performance liquid chromatography with a Hewlett Packard HP 1090 Liquid Chromatography unit. The lower limit of sensitivity for this assay was 3.5 mcg/mL for ticarcillin and 0.2 mcg/mL for clavulanic acid, with a coefficient of variation of 3.4% for ticarcillin and 2.8% for clavulanic acid.

The pharmacokinetic parameters were determined by application of linear regression analysis through the use of a Sharp Scientific Calculator, Model EL-512, and the use of noncompartmental analysis based on statistical moment theory.[10] This method is based on the estimation of the area under the curve (AUC) of the plot of drug concentration versus time from time zero to infinity. It can be applied to any compartment model in which linear pharmacokinetics is assumed.

Area under the curve, from time zero to infinity, after a single intravenous dose was calculated through the use of the trapezoidal rule from the concentration-time data following drug administration.

$$AUC_{0-\infty} = \Sigma\left[\frac{C_{n-1} + C_n}{2} (t_n - t_{n-1}) \right] \frac{C_L}{K_{el}} \qquad \text{Equation 1}$$

Where n is the number of trapezoids into which the curve is divided, C is the plasma concentration, t is time, C_L is the last plasma concentration obtained and K_{el} is the terminal elimination rate constant.

Area under the moment curve (AUMC), from time zero to infinity, is also calculated through the use of the trapezoidal rule, but from the concentration x time versus time plot.

The concentration versus time data were analyzed by means of linear regression which determined the slope of the natural log of the plasma concentration versus time line. This slope is the terminal elimination rate constant K_{el}. The terminal (β) half-life ($t_{1/2}$) was calculated with the following equation:

$$t_{1/2} = 0.693/K_{el} \qquad \text{Equation 2}$$

Clearance (Cl) of the drug from the plasma is calculated from the intravenous dose (D_{iv}) and the AUC:

$$Cl = D_{iv}/AUC \qquad \text{Equation 3}$$

Apparent volume of distribution at steady state (V_{ss}) was calculated with the following equation.

$$V_{ss} = \frac{D_{iv} \cdot AUMC}{AUC^2} - \frac{D_{iv} \cdot T}{2\ AUC} \qquad \text{Equation 4}$$

where T is the length of infusion time.

The V_{ss} was also calculated on a weight, in kilograms, to correct for variation in body mass.

$$V_{ss}\ (L/kg) = \frac{V_{ss}\ (L)}{wt(kg)} \qquad \text{Equation 5}$$

The steady state trough plasma concentration (C_{min}) was estimated for repetitive doses administered at regular intervals with the following equation:

$$C_{min} = \frac{F \cdot D \cdot e^{-K_{el}\ \tau}}{V_{ss}\ (1-e^{-k_{el}\ \tau})} \qquad \text{Equation 6}$$

where F is the bioavailability, which for intravenous adminstration is one, and τ is the dosing interval.

During the pharmacokinetic study, data were also collected for the safety and efficacy of ticarcillin/clavulanic acid. Therapy with the study antibiotic was initiated at the time of the enrollment into the study. Subjects were treated for at least five days unless the response to therapy was unsatisfactory. If the subject did not improve after 48 hours of therapy, the subject was clinically and bacteriologically re-evaluated. The re-evaluation resulted in either discontinuation of the study treatment, with the beginning of a replacement therapy, or continuation of the trial. Subjects who received the study treatment for less than 48 hours were classified as clinically and bacteriologically unevaluable.

Subjects were monitored daily for significant events relating to the primary diagnosis and for adverse reactions to the study drug. Hematologic, blood chemistry and urine tests were performed during the immediate pretreatment period and were repeated periodically during treatment as well as when the treatment was discontinued. All laboratory tests resulting in presumed drug-related abnormal values were repeated one to two weeks following completion of treatment and at two week intervals thereafter until the values returned to normal or until the principal investigator, the primary physician and the clinical monitor from Beecham Laboratories agreed that further follow-ups were no longer clinically relevant for the subject.

Bacteriological assessments were made by repeating a culture of a specimen from the anatomic site(s) which was positive on initial culture. Bacteriological assessments of infections, other than urinary tract infections, included a repeat culture from an appropriate infected site or anatomic site 2 to 4 days after beginning

treatment. Cultures were repeated on the final day of treatment or within 5 days post-treatment, unless healing precluded the collection of ample specimen for bacteriological evaluation. For urinary tract infections, cultures were repeated 2 to 4 days after initiation of treatment and 5 to 9 days following the completion of treatment. Pathogens isolated from pretreatment cultures, the isolates obtained during treatment and during follow-up were identified and tested for susceptibility to ticarcillin and ticarcillin/clavulanic acid.

Upon completion of treatment, the infection was evaluated clinically and classified as cure, clinical improvement, failure or unevaluable. In the case of urinary tract infections, follow-up clinical assessments were completed and the infection was classified as clinically cured, relapsed or unevaluable. These terms are defined in Appendix 3. Each case was also evaluated bacteriologically. The pathogen was categorized as eliminated, effectively treated, persistent cure, reinfection, relapse, superinfection, failure or unevaluable. Definitions of these terms are in Appendix 4.

Each adverse event related to drug administration was recorded on a standardized case report form according to date, time of occurrence, type, severity (mild, moderate, or severe), duration and category of organ system affected.

Statistics

Individual and population pharmacokinetic characteristics were evaluated for correlation with such demographic and anthropometric data as age, weight and estimated creatinine clearance. Statistical significance was determined by use of Spearman's rank correlation with an *a priori* critical level of 0.05.

RESULTS

Population Description

Fifteen male subjects were enrolled in the study with fourteen subjects completing the study. The mean age (± standard deviation) was 75.1 years (±10.3 years, range 63 to 93 years). The age distribution of the 14 subjects that completed this study were five between the age of 60 and 69 years, five between the age of 70 and 79 years, one was between 80 and 89 years and three were between 90 and 99 years. The mean height was 70.3 inches (±2.8 inches, range 64 to 74 inches), and the mean weight was 65 kg (±10.2 kg, range 46 to 86.5 kg). Subject #6 was removed from the study upon request of his private physician and is not included in the results. Seven (7/14) subjects were previously on antimicrobial agents without clinical improvement and were admitted to the study under the assumption that the organisms were resistant to the original agent.

Pharmacokinetics

Pharmacokinetic characteristics were studied during the initial dosing interval in all subjects except Subject #5 in whom it was impossible to obtain peripheral venous blood samples at that time. The pharmacokinetic analysis of this subject was performed during the second day of therapy when it was possible to obtain blood samples through the femoral artery. No drug was detected in the predose blood sample, and since his parameters fall within one standard deviation of the mean of the group, his values were included in the results. There was an interference with the assay of ticarcillin in Subject #10, therefore his data were excluded from the ticarcillin pharmacokinetics.

Serum ticarcillin and clavulanic acid concentrations after intravenous administration are presented in Tables 2 and 3 and the graphs are found in Appendix 5. The pharmacokinetic parameters are presented in Tables 4 and 5. The mean (± SD) elimination rate constants for ticarcillin and clavulanic acid were 0.444 (±0.233) h^{-1} and 0.435 (±0.209) h^{-1}, respectively with the mean half-lives being 2.3 (±2.1) hours and 2.1 (±1.4) hours, respectively. Mean apparent volumes of distribution for ticarcillin and clavulanic acid calculated at steady state were 15.7 (±7.4) liters and 33.6 (±17.9) liters, respectively. When adjusted for body weight, the mean apparent volumes of distribution for ticarcillin and clavulanic acid were 0.25 (±0.14) liters per kilogram and 0.53 (±0.28) liters per kilogram, respectively. The mean plasma clearance were 6.8 (±4.7) liters per hour and 10.4 (±5.9) liters per hour, respectively. The mean areas under the curve for ticarcillin and clavulanic acid were 575.9 (±641.2) mcg-h/mL and 10.8 (±9.3) mcg-h/mL, respectively.

Trough serum concentrations to assess accumulation obtained after 48 and 96 hours of therapy are shown in Tables 6 and 7 along with the calculated minimum serum concentrations at steady state.

Spearman's rank correlation, a nonparameteric statistical test was performed relating age or creatinine clearance to plasma clearance of the drugs or drug half-life. There was a statistical significance of 0.046 for the correlation between the clearance of ticarcillin and the estimated creatinine clearance of the subjects, but the correlation value was 0.562 which was less than the level of 0.85 set as significant a priori. No statistically significant correlation was found between the other variables analyzed (see Table 8).

Efficacy

Fourteen infections in 13 subjects were treated with ticarcillin/clavulanic acid. Twelve subjects had a single identifiable source of infection, of these, no organisms were isolated in four subjects. One subject (#7) had two sources of infection, a urinary tract infection and bacteremia with the same organism. Another subject (#13) had three identifiable sources of infection, urinary tract, respiratory tract and blood, from which different organisms were cultured. One organism, Enterobacter cloacae, was resistant to ticarcillin/clavulanic acid, therefore therapy was changed to an appropriate antibiotic.

The types of infections treated included pneumonias (6/14), urinary tract infections (4/14), cellulitis (3/14), and bacteremia (1/14) (Table 2). The organisms cultured and their susceptibilities are found in Table 9. Gram positive genera cultured included Enterococcus, Streptococcus, and Staphylococcus. Gram negative genera included Citrobacter, Pseudomonas, Klebsiella, Escherichia, Haemophilus and Bordetella.

Of the gram positive organisms tested for susceptibility to both ticarcillin and ticarcillin/clavulanic acid, all (4/4) were susceptible to both antibiotics. There were nine gram negative organisms isolated. Four (4/9) organisms were resistant to ticarcillin alone, but were susceptible to ticarcillin/clavulanic acid and two organisms (2/9) were intermediately susceptible to ticarcillin alone but were susceptible to ticarcillin/clavulanic acid. Three organisms (3/9) were susceptible to both ticarcillin and ticarcillin/clavulanic acid (see Table 10).

Clinical results of the 14 subjects, as monitored by resolution of physical signs and symptoms included seven cures (7/14), four improvements (4/14), one subject was unevaluable (1/14) one failure (1/14), and one was excluded because his infecting organism was resistant to ticarcillin/ clavulanic acid (1/14). Bacteriological improvement, as evaluated by culture, for the 14 subjects included seven cures, and one relapse with a urinary tract infection (UTI). There was no isolation of organisms in three subjects, no specimen available for culture in two subjects and one subject was excluded because of a resistant organism.

Safety

Ticarcillin/clavulanic acid therapy was well tolerated by most subjects. One subject (#11) had erythema and edema at the administration site which resolved within 36 hours after changing the administration site. One subject (#9) complained of mild nausea during the administration of the drug. This complaint resolved without discontinuing therapy. Another subject (#10) had an increase in blood pressure on the last day of therapy.

DISCUSSION

Pharmacokinetics

The pharmacokinetic characteristics of ticarcillin in healthy male volunteers of unspecified age have been studied by Libke et al.[11] Bodey et al studied the combination of ticarcillin/clavulanic acid in 15 female cancer patients with infections, ages 34 to 67 years and Bennett et al reported the pharmacokinetics of this combination in six male volunteers between the ages of 24 and 40 years.[12,13] The present study differs from the above studies in that

the population sample studied was limited to elderly subjects with an age distribution of 63 to 93 years.

Ticarcillin is distributed in tissue and interstital fluid with a mean apparent volume of distribution at steady state of 10.8 to 15.0 liters, reported in the literature.[11,12,13] A decrease in the apparent volume of distribution would be expected in elderly subjects due to the decrease in the percent of total body water which occurs with aging.[8] Also, there is a decrease in the proportion of muscle mass with respect to the total body mass. In this study, the mean apparent volume of distribution at steady state for ticarcillin was slightly greater (15.7 liters) than the mean of 10.8 to 14.6 liters reported in the above studies. The subjects in this study had considerable variation in this parameter, ranging from 7.3 liters to 29.8 liters. The mean apparent volume of distribution at steady state for ticarcillin, adjusted for weight was 0.25 (±0.14) liters per kilogram. The mean apparent volume of distribution at steady state for clavulanic acid reported in literature is 20.3 and 22.3 liters.[12,13] In this study, the mean of 33.6 (±17.9) liters was greater than that reported in the current literature. Table 11 contains a comparison of the results of this study and the studies of Bodey et al and Bennett et al. Both of the drugs have a larger volume of distribution than one would expect in elderly subjects with drugs which are distributed mainly into body tissue and interstital fluid. This may illustrate the large degree of variability often seen in the elderly, the sample size, or inaccuracies in the sampling and/or the assay technique.

Clearance of renally excreted drugs, such as ticarcillin which is 99% renally excreted, would be expected to decrease in the elderly due to the trend of decreased renal function with aging.[14,15,16] Parry and Neu reported that the half-lives of ticarcillin were prolonged in the presence of renal dysfunction as reflected by a decrease in creatinine clearance (CrCl).[17] Subjects with normal renal function, as defined by a CrCl > 60 ml/min, had a half-life of 1.18 (±0.1) hours. This is consistent with the half-lives reported by Bennett and Bodey in the studies with ticarcillin/clavulanic acid.[12,13] Subjects with mild to moderate renal insufficiency (CrCl 30-60 mL/min) had a half-life of 3.0 (±0.6) hours and subjects with a CrCl of 10-30 mL/min had a prolonged half-life of 8.5 (±2.1) hours. The mean half-life of ticarcillin for this study in the elderly subjects was 2.3 (±2.1) hours. When the results are grouped according to creatinine clearance, the results are similar to the results of Parry and Neu except for a lower half-life for the one subject with a CrCl between 10 and 30 mL/min (see Table 12).[17]

The half-life for clavulanic acid has not been studied in renal dysfunction. Since clavulanic acid is metabolized by the liver, with only 20 to 60% excreted unchanged in the urine, the half-life is not expected to change with renal impairment.[18,19] This is consistent with the results of our study when the results were grouped according to creatinine clearance (see Table 12).

The plasma clearance of ticarcillin reported by Bennett et al and Bodey et al were 7 (±2.5) L/h and 6.9 (±2.2) L/h, respectively.[12,13] The plasma clearance observed in our sample of elderly subjects was 6.5 (±4.7) L/h. Plasma clearance for clavulanic

acid reported by Bennett et al and Bodey et al was 14.5 (±3.70) and 10.2 (±3.5) L/h, respectively.[12,13] The findings of our study is comparable at 10.4 (±5.9) L/h.

The trough data for assessment of possible accumulation are difficult to evaluate. Accumulation would be expected until steady state was achieved, since a loading dose was not administered. If the steady state troughs were obtained appropriately, they should compare to a calculated minimum plasma concentration (see Equation 6). The majority of ticarcillin and clavulanic acid troughs obtained at 48 and 96 hours were greater than the calculated minimum serum concentrations (see Tables 6 and 7). Possible explanations for this apparent accumulation of drug in the present study would include sampling errors, assay limitations or changes in drug disposition. The accuracy of the dosing interval due to variations in administration times was not controlled in this study. The administration time of the dose prior to the trough was not witnessed by one of the investigators and the exact administration times were not recorded in the medication administration record, therefore, accurate troughs may not have been obtained. Changes in the distribution, metabolism and excretion of the drug may also account for the apparent accumulation. Factors that influence the drug disposition would include acute changes in renal function, disease states or concurrent drugs usage that would decrease excretion or metabolism of the drugs or change the distribution of drugs. The renal function, as measured by serum creatinine, did not decline while the subjects were on the study drug. Except for the infections being treated, the disease states of

the subjects remained stable. Subjects were not begun on any medications during the treatment period that decreased the excretion of the drugs by kidneys. Liver function tests did not imply changes in the liver function, which is the site of metabolism of clavulanic acid. Even though there was an apparent accumulation of the drugs in this study, adverse reactions to the study drug were infrequent.

A possible explanation for the differences in the pharmacokinetic characteristics in the elderly subjects found in this study as compared to prior literature, include differences in the type of laboratory analysis used, errors in estimating the elimination rate constant and the changing status of the subjects due to the seriousness of their presenting illnesses. The high performance liquid chromatography assay used for the clavulanic acid data was developed for this study. Until this time, the assay used was a microbiological assay. A difference in clavulanic acid results compared to the literature could be explained in part by the different assays. There was at least one case of interference in the ticarcillin assay and this may have occurred to a lesser degree in other subject's samples. Errors in estimating the elimination rate constant is another possible explanation. This parameter was estimated from a regression line of the plasma concentration versus time plot. The points selected to be included in this line could reflect a limitation in this estimate. The elimination rate constant was used to calculate the other pharmacokinetic parameters. Another factor which could affect the pharmacokinetic characteristics of this study was the changing status of subjects due to seriousness of their presenting illnesses. These subjects, unlike "normal volunteers", had

underlying chronic diseases or conditions (such as dehydration, decreased renal function, and shock), concommitant medication and presenting illnesses that were serious enough to require hospitalization. These multiple factors may influence how elderly persons respond to a drug and may cause changes in their pharmacokinetic characteristics.

One other factor could be that ticarcillin or clavulanic acid disposition does not follow first order pharmacokinetics in this population. Dose-dependent pharmacokinetics have been reported with the acylureido penicillins, mezlocillin, piperacillin and azlocillin, but not specifically in the elderly.[20] Nonlinearity has not been reported to date with ticarcillin or clavulanic acid.

An interesting finding in this study was that the standard deviations for the parameters were greater in this study conducted in an elderly sample population than those reported in the literature. This may reflect the sample size, assay limitations or the heterogenicity of the sample population.

The Spearman's rank correlation statistic was statistically significant for the clearance of ticarcillin and the estimated creatinine clearance, but showed only a moderate correlation. The clinical significance of these results suggests that it is important to adjust the dosage of ticarcillin/clavulanic acid in renal dysfunction.

Efficacy

Barry et al, compared the in vitro susceptibility of organisms to ticarcillin alone and ticarcilin/clavulanic acid.[21] Seventy percent of the Enterobacteriaceae species were susceptible to ticarcillin alone and 91% were susceptible to ticarcillin/clavulanic acid.

Bacteroides fragilis and Bacteroides melaninogenicus isolates were also more susceptible to the combination than to ticarcillin alone. Fuch et al, tested clinical bacterial isolates for susceptibility to ticarcillin alone and in combination with clavulanic acid. An eightfold or greater decrease in MICs was found in 92% of Enterobacteriaceae with ticarcillin MICs ≥ 64 mcg/mL.[22] Ticarcillin MICs for β-lactamase producing Haemophilus influenzae, Neisseria gonorrhoeae and most Staphylococcus aureus were reduced to ≤ 0.5 mcg/mL with the addition of clavulanic acid. The change in MICs for Pseudomonas species was minimal. Chattopadhyay and Hall tested the in-vitro activity of ticarcillin/clavulanic acid against ticarcillin resistant gram negative bacilli.[23] Resistance was defined as an MIC ≥ 128 mcg/mL. The combination had enhanced activity against the Proteus species, Escherichia coli and Klebsiella species isolates compared to ticarcillin, by decreasing the MIC's to ≤ 64 mcg/mL.

Clarke and Zemcov compared the combination of ticarcillin/clavulanic acid with other β-lactam antibiotics including ampicillin, piperacillin and cefotaxime.[24] The ticarcillin/clavulanic acid combination was as active or more active than piperacillin against most members of the Enterobacteriaceae genera, such as Escherichia coli, Klebsiella pneumoniae, Proteus mirabilis and Providencia stuartii. The ticarcillin/clavulanic acid combination was considerably more active against Staphylococcus aureus, Haemophilus influenzae and Bacteroides fragilis than ticarcillin alone or piperacillin. Of the agents studied, cefotaxime was the most active against Haemophilus influenzae and piperacillin was the most active against Pseudomonas aeruginosa. In summary, the in vitro activity of the

combination of ticarcillin/clavulanic acid exceeds the activity of ticarcillin, mostly for the Enterobacteriaceae species. The combination does not exceed ticarcillin's activity against Pseudomonas aeruginosa.

The efficacy and safety of the combination of ticarcillin/clavulanic acid have been investigated in the treatment of hospitalized patients with bacterial infections. Roselle et al, treated 50 episodes of infection in 43 patients, ages 62 (±11) years.[25] The infections included pneumonia, bacteremia, urinary tract infection and osteomyelitis. Of the 50 episodes treated there were 44 clinical cures. Five patients improved clinically without cultures becoming negative, and one patient failed to improve with treatment with ticarcillin/clavulanic acid.

File et al, randomly compared the combination of ticarcillin/clavulanic acid to piperacillin or moxalactam in the treatment of acute bacterial infections.[26] There were 91 clinically evaluated infections. A satisfactory clinical response, defined as cure or significant improvement of presenting signs and symptoms, occurred in all 46 patients treated with ticarcillin/clavulanic acid, in 27 of the 28 patients treated with piperacillin and 14 of the 16 patients treated with moxalactam.

Based on these results, ticarcillin/clavulanic acid has been approved for the treatment of bacterial septicemia, including bacteremia, lower respiratory infection, bone and joint infections, skin and skin structure infections and urinary tract infections caused by susceptible strains of organisms.[27] Even though the addition of clavulanic acid increased the spectrum of activity of ticarcillin,

this combination should be used as an alternative antibiotic for resistant organisms rather than the drug of choice, due to the cost of the product.

Safety

Roselle et al reported that adverse drug reactions to ticarcillin/clavulanic acid were similar to ticarcillin alone.[25] File et al, stated that adverse reactions were uncommon in their study.[26] Local reactions at the site of administration and nausea each occurred in separate subjects in this study, both of these reactions are reported in the product information.[27] There is a sodium content of 4.75 mEg per gram of Timentin®, which could have contributed to the increase in blood pressure in subject #10 on the final day of therapy.

CONCLUSIONS

The pharmacokinetic characteristics, safety and efficacy of ticarcillin/clavulanic acid were studied in hospitalized elderly subjects. The differences in the mean pharmacokinetic characteristics of ticarcillin included a prolonged half-life, with a slightly larger volume of distribution and lower clearance than reported in the literature for the combination of ticarcillin and clavulanic acid in younger subjects. Differences in the clavulanic acid mean pharmacokinetic characteristics included a prolonged half-life and an increased volume of distribution. When dosing ticarcillin/clavulanic acid in elderly patients it is important to adjust the dosage according to the renal function of the individual.

TABLES

TABLE 1: TIMENTIN® DOSAGE RECOMMENDATIONS FOR RENAL INSUFFICIENCY[27]

Creatinine Clearance[a]	Dose	Frequency
Over 60 mL/min	3.1 gm	Every 4 hours
30-60 mL/min	2 gm[b]	Every 4 hours
10-30 mL/min	2 gm[b]	Every 8 hours
< 10 mL/min	2 gm[b]	Every 12 hours
< 10 mL/min with hepatic dysfunction	2 gm[b]	Every 24 hours
Patients on peritoneal dialysis	3.1 gm	Every 12 hours
Patients on hemodialysis	2 gm[b] + 3.1 gm	Every 12 hours After each dialysis

[a]Creatinine Clearance calculated from serum creatinine using the following equation:

$$CrCl = \frac{(140 - \text{age}) \text{ wt in kg}}{72 \times \text{serum creatinine}} \quad \text{(for males)}$$

Crockcroft DW et al. Nephron 1976;16:31-41.

[b]Based on ticarcillin content

TABLE 2: TICARCILLIN SERUM CONCENTRATIONS (mcg/mL)

Subject #	Predose	5 min @	15 min	30 min	60 min	90 min	120 min	240 min	360 min
1	ND	151	150	101	88.5	78.2	67.5	53.2	-
2	ND	202	193	185	168	-	116	64	43
3	ND	165	144	131	101	82	67	33	-
4	ND	488	260	208	-	151	117	-	-
5	ND	168	-	150	121	-	95	ND	-
7	ND	134	128	115	81	66	53	-	-
8	ND	93	80	70	52	46	38	18	-
9	ND	164	-	104	93	67	62	46	-
11	ND	145	122	90	52	39	ND	55	-
12	ND	124	105	95	68	50	48	50	-
13	ND	204	184	185	177	170	164	152	-
14	ND	242	221	178	117	74	51	ND	-
15	ND	140	114	94	79	64	55	205	-

ND = Not detected
@ = Approximate time blood sample obtained
- = Serum concentration not obtained

TABLE 3: CLAVULANIC ACID SERUM CONCENTRATIONS (mcg/mL)

Subject #	Predose	5 min@	15 min	30 min	60 min	90 min	120 min	240 min	360 min
1	ND	2.2	2.2	1.7	1.6	1.5	1.3	ND	-
2	ND	4.2	3.5	3.1	2.7	-	1.8	1.1	0.8
3	ND	5.0	3.6	3.1	2.3	1.6	1.1	0.3	-
4	ND	7.6	2.8	2.1	-	1.5	0.9	-	-
5	ND	1.7	-	2.8	2.3	-	2.0	1.2	-
7	ND	2.7	2.2	2.1	1.5	1.1	ND	-	-
8	ND	2.0	1.3	1.0	0.8	0.7	0.5	ND	-
9	ND	7.1	-	2.6	1.9	1.3	1.1	0.6	-
10	ND	3.2	2.7	2.4	2.1	1.8	1.8	1.5	-
11	ND	4.2	3.3	2.2	1.6	1.4	1.1	-	2.8
12	ND	4.3	3.7	3.1	1.8	1.2	0.6	0.3	-
13	ND	7.6	6.7	6.0	5.5	5.0	4.6	3.4	-
14	ND	5.5	4.5	3.8	2.5	1.9	1.3	0.6	-
15	ND	4.0	3.4	2.8	1.9	1.5	1.2	7.3	-

ND = Not detected
@ = Approximate time blood sample obtained
- = Serum concentration not obtained

TABLE 4: TICARCILLIN PHARAMCOKINETIC DATA

Subject #	Kel h^{-1}	t 1/2 h	AUC mcg h/mL	AUMC mcg h^2/mL	CL L/h	Vss liter	Vss/wt L/kg
1	0.240	2.89	582.26	4271.38	3.43	24.34	0.32
2	0.296	2.34	755.31	3993.46	2.65	13.34	0.21
3	0.435	1.59	388.70	1196.95	5.15	14.56	0.24
4	0.429	1.62	661.34	1609.30	4.54	9.88	0.15
5	0.305	2.27	561.79	2271.36	3.56	13.50	0.21
7	0.513	1.35	276.53	348.20	7.20	7.30	0.12
8	0.377	1.84	217.86	760.76	9.18	29.76	0.63
9	0.374	1.85	417.73	1796.05	4.79	19.39	0.26
11	0.917	0.76	155.78	134.93	19.26	11.87	0.18
12	0.608	1.14	224.11	384.32	8.92	13.07	0.18
13	0.077	9.00	2619.61	26,734.65	1.15	11.41	0.22
14	0.846	0.82	311.98	329.40	9.60	7.75	0.13
15	0.359	1.93	313.88	993.43	9.56	27.86	0.46
mean	0.444	2.267	575.914	3448.015	6.845	15.695	0.255
SD	0.233	2.112	641.153	7122.430	4.689	7.378	0.144

Kel = elimination rate constant
T 1/2 = terminal half-life
AUC = area under the curve
AUMC = area under the moment curve
CL = plasma clearance
Vss = apparent volume of distribution at steady state
Vss/wt = apparent volume of distribution at steady state adjusted for weight

TABLE 5: CLAVULANIC ACID PHARAMCOKINIETIC DATA

Subject #	Kel h^{-1}	t 1/2 h	AUC mcg h/mL	AUMC mcg h^2/mL	CL L/h	Vss liter	Vss/wt L/kg
1	0.129	5.37	13.89	177.41	4.82	60.4	0.81
2	0.307	2.26	12.81	72.97	5.23	28.49	0.45
3	0.660	1.05	7.93	10.11	8.45	8.66	0.14
4	0.619	1.12	5.56	7.54	17.54	19.9	0.29
5	0.241	2.88	12.16	94.58	5.51	41.48	0.66
7	0.619	1.12	4.40	6.06	15.23	17.17	0.28
8	0.448	1.55	2.93	6.54	22.87	45.32	0.99
9	0.586	1.18	7.77	11.82	8.62	10.96	0.14
10	0.240	2.89	13.73	118.23	4.88	40.8	0.47
11	0.249	2.78	9.52	59.66	10.5	60.2	0.94
12	0.764	0.91	5.23	22.94	12.81	57.89	0.79
13	0.157	4.40	40.78	585.80	2.45	34.61	0.65
14	0.532	1.30	8.72	17.91	11.47	20.69	0.34
15	0.55	1.26	6.40	11.34	15.6	23.78	0.4
mean	0.4357	2.148	10.845	85.922	10.927	33.6	0.525
SD	0.2093	1.375	9.311	153.031	5.859	17.866	0.283

Kel = elimination rate constant
T 1/2 = half life
AUC = area under the curve
AUMC = area under the moment curve
CL = plasma clearance
Vss = apparent volume of distribution at steady state
Vss/wt = apparent volume of distribution at steady state adjusted for weight

TABLE 6: TROUGH DATA FOR TICARCILLIN (mcg/mL)

Subject #	48 Hr Trough	96 Hr Trough	Minimum Concentration
1	115	172.5	51
2	64	189	30
3	--	--	29
4	--	105	67
5	73	37	62
7	--	83	40
8	110	92	19
9	108	105	30
11	ND	28	1
12	74	ND	14
13	--	--	
14	ND	ND	14
15	93	115	34

ND = not detected

-- = not obtained

TABLE 7: TROUGH DATA FOR CLAVULANIC ACID (mcg/mL)

Subject #	48 Hr Trough	96 Hr Trough	Minimum Concentation
1	1.7	4.4	1.6
2	1.6	4.1	0.4
3	0.3	1.4	0.6
4	--	0.8	0.5
5	0.6	0.2	1
7	--	ND	0.4
8	0.8	1.7	0.3
9	2.1	1.9	0.6
10	2.3	1.9	1
11	0.7	0.3	0.3
12	0.9	0.5	0.1
13	5.7	--	3.3
14	0.3	--	0.7
15	2.4	2.5	0.5

ND = not detected

-- = not obtained

TABLE 8: SPEARMAN'S RANK CORRELATION

Variable #1	Variable #2	Correlation Value (r)	Significance (p)
Age	Adj. CrCl*	-0.5	0.067
Age	Clearance - Ticarcillin	-0.3	0.362
Age	T 1/2 - Ticarcillin	0.5	0.074
Adj. CrCl	T 1/2 - Ticarcillin	-0.4	0.212
Age	Clearance - Clav. Acid	-0.2	0.45
Age	T 1/2 - Clav. Acid	0.3	0.347
Adj. CrCl	Clearance - Clav. Acid	0.1	0.754
Adj. CrCl	T 1/2 - Clav. Acid	0.1	0.823
T 1/2 - Ticarcillin	Est. CrCl ^	-0.46	0.114
Clearance - Ticarcillin	Est. CrCl	0.562	0.046
T 1/2 - Clav. Acid	Est. CrCl	0.019	0.95

* = CREATININE CLEARANCE ADJUSTED FOR BODY SURFACE AREA
^ = CREATININE CLEARANCE ESTIMATED FROM CROCKCROFT EQUATION
$r \geq 0.85$ for correlation
$p \leq 0.05$ for significance

TABLE 9: NUMBER OF ORGANISMS PER TYPE OF INFECTION

TYPES OF INFECTIONS	NO ORGANISMS	1 ORGANISM	2 ORGANISMS	3 ORGANISMS	TOTALS
Pneumonia	1	3	2	0	6
Cellulitis	2	0	0	1	3
Urinary tract	1	2	0	1	4
Bacteremia	0	1	0	0	1
TOTALS	4	6	2	2	14

TABLE 10: SUSCEPTIBILITY OF ISOLATED BACTERIA

ORGANISMS IDENTIFIED	TIMENTIN Disk Zone Size (mm)	TICARCILLIN Disk Zone Size (mm)
Gram Positive		
Enterococcus (2)	19 (S)	21 (S)
	21 (S)	21 (S)
Streptococcus pneumoniae (2)	43 (S)	43 (S)
	45 (S)	45 (S)
Gram Negative		
Citrobacter diversus	27 (S)	14 (I)
Pseudomonas maltophilia	15 (S)	7 (R)
Klebsiella pneumoniae (2)	25 (S)	9 (R)
	26 (S)	14 (I)
	23 (S)	N/D
Escherichia coli (4)	17 (S)	6 (R)
	17 (S)	6 (R)
	29 (S)	31 (S)
	24 (S)	26 (S)
Haemophilus influenzae	N/D	N/D
Bordetella bronchiseptica	31 (S)	22 (R)

R = resistant = ≤ 11 mm
I = intermediate = 12 - 14 mm
S = susceptible = ≥ 15 mm

N/D = not done
TIMENTIN = 75 mcg ticarcillin plus 10 mcg clavulanic acid/disk
( ) = number of times organisms were isolated

TABLE 11: MEAN (± SD) PHARMACOKINETIC PARAMETERS FOR TICARCILLIN AND CLAVULANIC ACID

PARAMETER	AUTHOR	TICARCILLIN	CLAVULANIC ACID
$t_{1/2\beta}$ (h)	Bennett[13]	1.1 (±0.1)	1.5 (±0.5)
	Bodey[12]	1.3 (±0.5)	1.4 (±0.4)
	Present Study	2.3 (±2.1)	2.1 (±1.4)
AUC (μg·h/mL)	Bennett	475 (±169)	14.6 (±3.7)
	Bodey	631 (±189)	11.0 (±3.0)
	Present Study	575.9 (±641.2)	10.8 (±9.3)
V_{ss} (liters)	Bennett	10.8 (±43)	20.3 (±8.0)
	Bodey	14.6 (±4.7)	22.3 (±3.2)
	Present Study	15.7 (±7.4)	33.6 (±17.9)
Cl (L/h)	Bennett	12.1 (±2.4)	20.9 (±3.7)
	Bodey	6.9 (±2.2)	10.2 (±3.5)
	Present Study	6.8 (±4.7)	10.4 (±5.9)

$t_{1/2\beta}$ = elimination half-life
AUC = area under the curve
V_{ss} = apparent volume of distribution at steady state
Cl = clearance

TABLE 12: MEAN (± SD) HALF-LIFE COMPARED TO CREATININE CLEARANCE

CrCl (mL/min)	>60	30-60	10-30	<10
TICARCILLIN				
Parry, Neu[17]	1.28(±0.1)h	3.0(±0.6)h	8.5(±2.1)h	14.8(±3.7)h
Present Study	1.3(±1.1) [n=3]	3.3(±3.0) [n=9]	2.34 [n=1]	
CLAVULANIC ACID				
Present Study	2.3(±0.9)	2.2(±1.7)	2.3	

*Subject #4 was excluded because his calculated CrCl of 242 mL/min was uninterpretable

APPENDICIES

APPENDIX 1

Subject Consent Form

CONSENT FOR PARTICIPATION IN INVESTIGATIONAL STUDY

I. INFORMATION ABOUT THE EVALUATION OF THE EFFICACY, SAFETY, AND PHARMACOKINETICS OF TIMENTIN IN THE TREATMENT OF BACTERIAL INFECTIONS IN ELDERLY PATIENTS.

Your doctors believe that you have a bacterial infection that should be treated with an antibiotic. There are several antibiotics that could be used to treat your infection. We are conducting research evaluating a newly released antibiotic, Timentin, which has been used to treat over 3000 adults. If you choose to participate in our study, you will be treated with Timentin which is given through veins.

The length of your treatment will depend upon your physician's assessment of your response to therapy, approximately 5-21 days. This antibiotic may potentially cause skin rash, gastrointestinal upset, and fever. These side effects are temporary and disappear when the antibiotic is stopped. If there is any evidence that your infection is not being controlled by Timentin, or you are experiencing significant unpleasant side effects, Timentin will be discontinued. Another antibiotic will be given to you in its place. Before, during and after treatment with this medicine it will be necessary to obtain blood samples which help us to evaluate the safety and effectiveness of the medicine. The amount of blood needed for each of these evaluations is approximately equal to one tablespoon. Also, following the first dose of Timentin blood, equivalent to 2 teaspoonfuls, will be obtained over a four to six hour period for the pharmacokinetic portion of the study. This portion of the study will be performed only if a venous catheter line "hep lock" is in place and functional. The total amount of blood obtained for the entire study is approximately 4 tablespoonfuls.

If you choose not to participate in the study, you will be treated with another antibiotic of your doctor's choice. If you choose to participate, you may withdraw from the study at any time, and this will not affect any further treatment you will receive.

A benefit for participating in this study, is that there will be no charge to you or to the hospital for the antibiotic or those laboratory tests performed which are for our monitoring of the antibiotic.

Questions about the medicine will be answered by Dr. Higbee or Dr. Wood, the principal investigators, or their colleagues. Drs. Higbee and Wood can be reached through the Veteran's Administration Medical Center Operator, 582-1565 ext. 1018. Any questions concerning your rights as a study participant can be answered by the University of Utah Institutional Review Board office, 581-3655.

Medical treatment or compensation for physical injury: In the event you sustain physical injury resulting from the research project in which you are participating, the University of Utah will provide you, without charge, emergency and temporary medical treatment not

otherwise covered by insurance. Furthermore, if your injuries are caused by negligent acts or omissions of University employees acting in the course and scope of their employment, the University may be liable, subject to limitations prescribed by law, for additional medical costs and other damages you sustain. If you believe that you have suffered a physical injury as a result of participation in this research program, please contact the Office of Research Administration, phone number 581-6903.

II. CONSENT

I acknowledge that I have had a fair opportunity to ask questions about the above study and upon consideration of the possible benefits and risk of the study as outlined, I give my consent to participate in this study.

I understand that I may withdraw my consent at any time without affecting the treatment I will receive.

I give my permission for information from my medical records to be released to Dr. Martin Higbee, Dr. James Wood, Beecham Laboratories, and the United States Food and Drug Administration, with the understanding that my identity will not be revealed unless I expressly consent thereto. I acknowledge receipt of a copy of this consent document.

_____

Signature of Patient Date

In the event that the study subject is incapable of providing informed consent:

I _____, a legal guardian of

_____ authorize his/her participation in this study.

_____

Signature of Legal Guardian Date

_____

Relationship

_____

Signature of Witness Date

_____

Principal Investigator's Signature

"An Evaluation of the Efficacy, Safety, and Pharmacokinetics of Timentin in the Treatment of Bacterial Infections in Elderly Patients".

APPENDIX 2

Diagnostic Criteria

APPENDIX 2: DIAGNOSTIC CRITERIA

1) Lower Respiratory Tract Infections: Pretreatment cultures were isolated from bronchopulmonary secretions obtained by one of the following methods: deep expectoration by a cooperative patient, catheter intubation with endotracheal suction, bronchoscopy, or transtracheal aspiration. The organisms isolated from the specimen were tested for susceptibility to ticarcillin/ clavulanic acid. A chest x-ray was also obtained prior to initiation of therapy with the study drug.

2) Skin or Skin Structure Infections: Specimens for culture were collected by aseptic aspiration below the surface of an abscess or joint cavity or by collecting a swab of purulent material from the site of infection. When the swab technique was used, precautions were employed to avoid contamination of the specimen with skin flora.

3) Septicemia: Isolation of a pathogenic organism was isolated from two (2) pretreatment blood cultures whenever possible. If a single specimen was all that could be collected, and it was of sufficient volume, the sample was divided and an analysis of each portion was performed.

4) Urinary Tract Infection: At least one (1) pretreatment culture was obtained with one or more pathogens, each of which is present with a colony count of 100,000 or more microorganisms per mL of urine.

APPENDIX 3

Clinical Assessment Criteria

APPENDIX 3: CLINICIAL ASSESSMENT CRITERIA

1) Clinical assessment at completion of therapy. Each case was classified into one of the following categories:

   a) Cured Clinically: The subject was asymptomatic and demonstrated significant improvement of physical signs.

   b) Clinically Improved: Clinical findings subsided significantly in a reasonable period of time but there was incomplete resolution of evidence of infection/ inflammation.

   c) Failure: No apparent response to therapy.

   d) Unevaluable: Negative pretreatment cultures, administration of concomitant antibiotics to which the pathogen was susceptible, insufficient duration of treatment, or failure to adhere to protocol.

2) Follow-up Clinical Assessment (Applicable to UTI only)

   a) Cured Clinically: The subject was asymptomatic.

   b) Relapse: Recurrence of initial symptoms of infection.

   c) Unevaluable: as above.

APPENDIX 4

Bacteriological Evaluation Criteria

APPENDIX 4: BACTERIOLOGICAL EVALUATION CRITERIA

Each case was classified into one the following categories for bacteriological evaluation:

1) Elimination: The pretreatment pathogen(s) was absent from the post-treatment culture specimen(s).

2) Effective: The specimen(s) which contained the pretreatment pathogen(s) was not obtainable following treatment due to clinical resolution.

3) Persistent Cure: The pretreatment pathogen(s) was absent from both post-treatment and follow-up cultures.

4) Reinfection: The pretreatment pathogen(s) was absent at the end of the treatment period but a different pathogenic species was present in the post-treatment or follow-up specimen.

5) Relapse: The pretreatment pathogen(s) was absent at the end of treatment but appeared again in the post-treatment or follow-up periods.

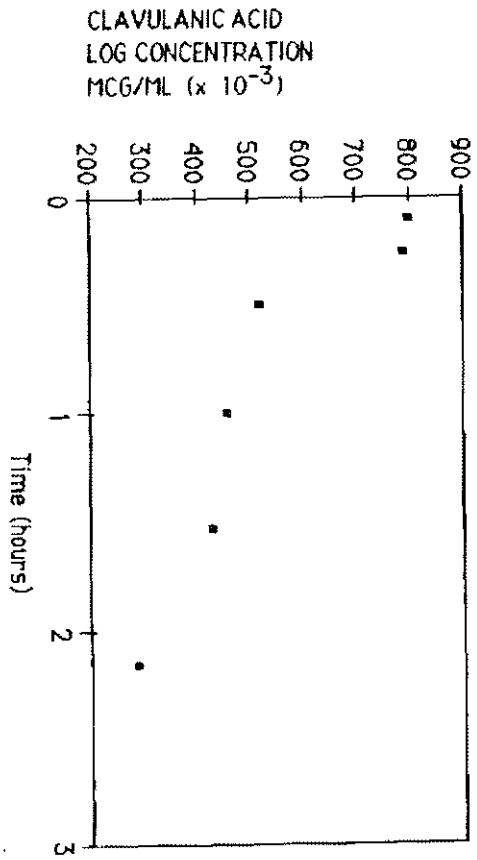
6) Superinfection: The pretreatment pathogen(s) was absent at the end of treatment with one or more different pathogenic species appearing during treatment and present at the end of treatment.

7) Failure: The pretreatment pathogen(s) was still present at the end of the treatment.

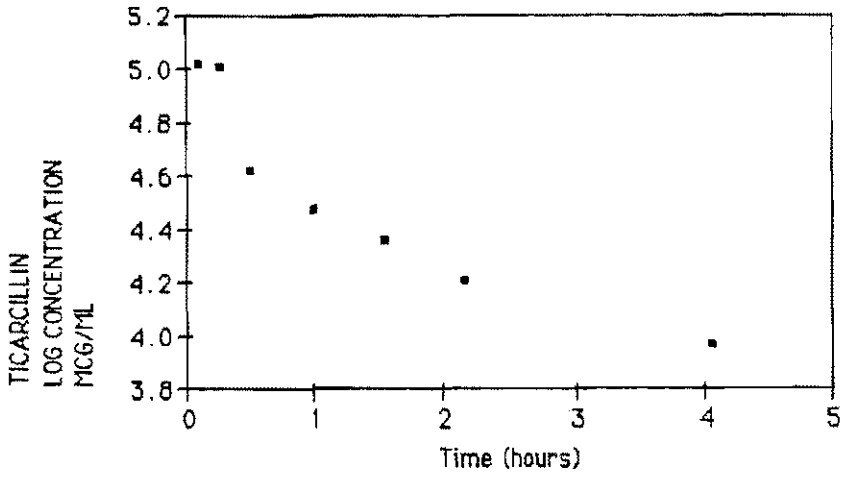
8) Unevaluable: As above.

APPENDIX 5

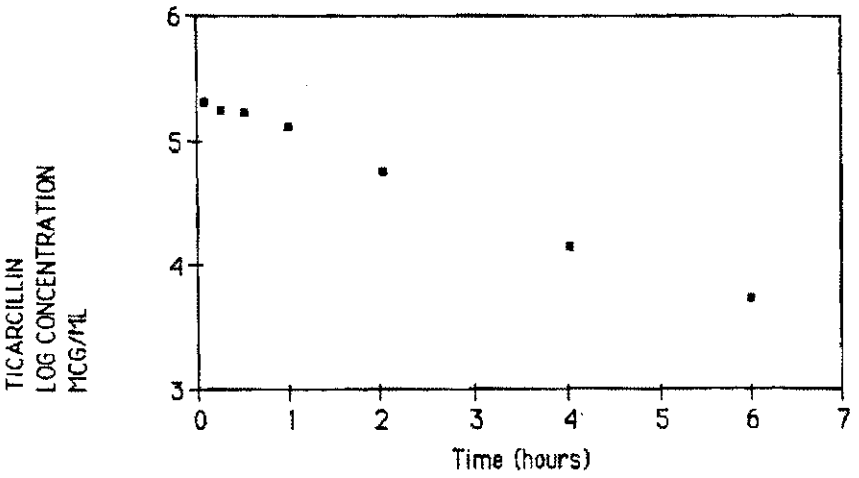
Log Plasma Concentration Versus Time Graphs

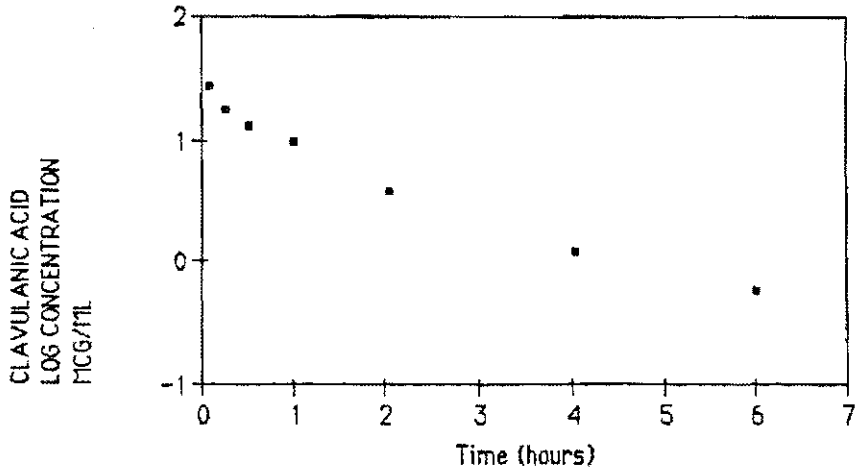

CLAVULANIC ACID
LOG CONCENTRATION
MCG/ML (x 10^{-3})
200
300
400
500
600
700
800
900
0
1
2
3
Time (hours)

SUBJECT #1

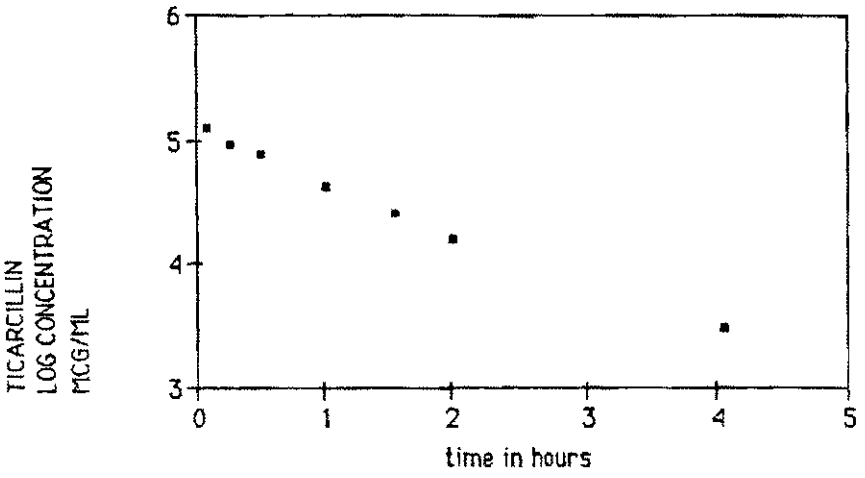

TICARCILLIN
LOG CONCENTRATION
MCG/ML
5.2
5.0
4.8
4.6
4.4
4.2
4.0
3.8
0
1
2
3
4
5
Time (hours)

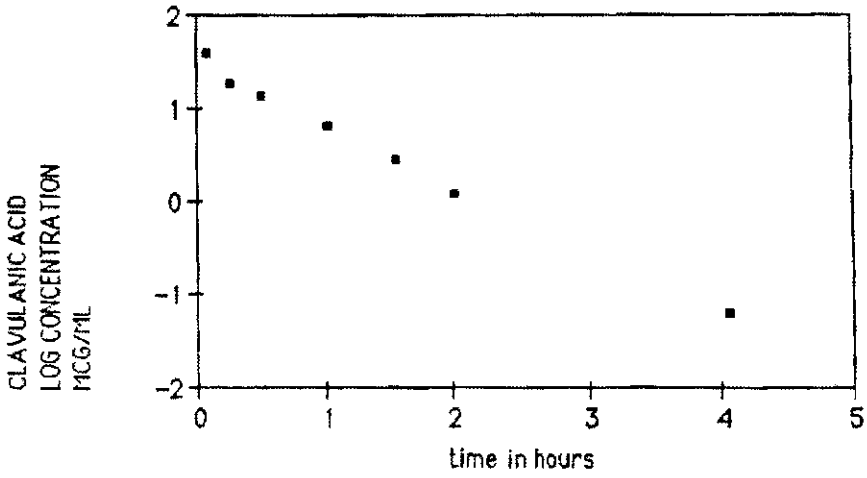
SUBJECT #2


TICARCILLIN
LOG CONCENTRATION
MCG/ML
6
5
4
3
0
1
2
3
4
5
6
7
Time (hours)


CLAVULANIC ACID
LOG CONCENTRATION
MCG/ML
2
1
0
-1
0
1
2
3
4
5
6
7
Time (hours)

SUBJECT #3


TICARCILLIN
LOG CONCENTRATION
MCG/ML
6
5
4
3
0
1
2
3
4
5
time in hours


CLAVULANIC ACID
LOG CONCENTRATION
MCG/ML
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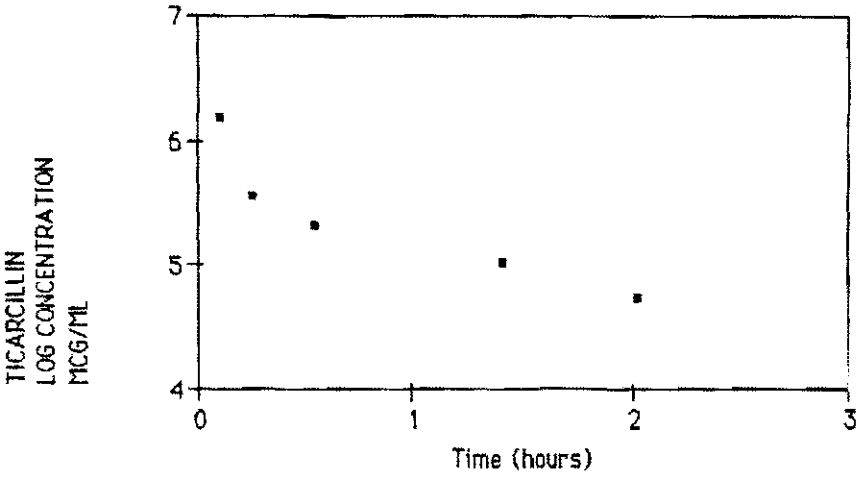
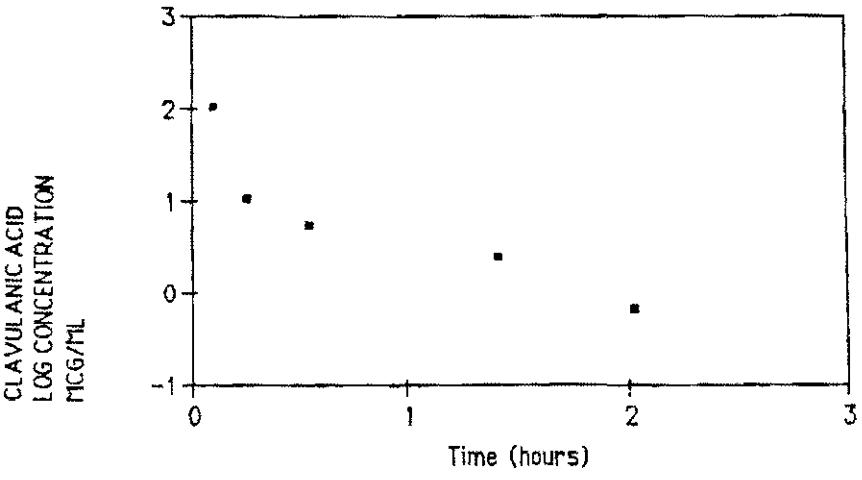
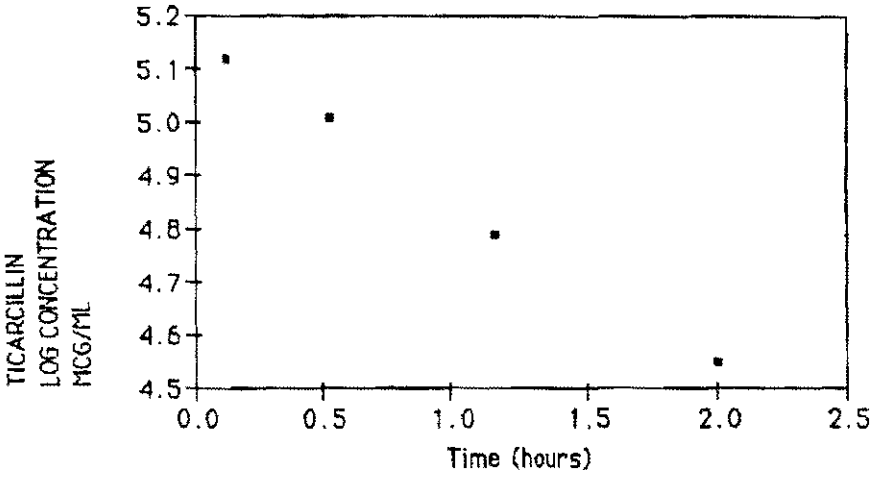
1
0
-1
-2
0
1
2
3
4
5
time in hours

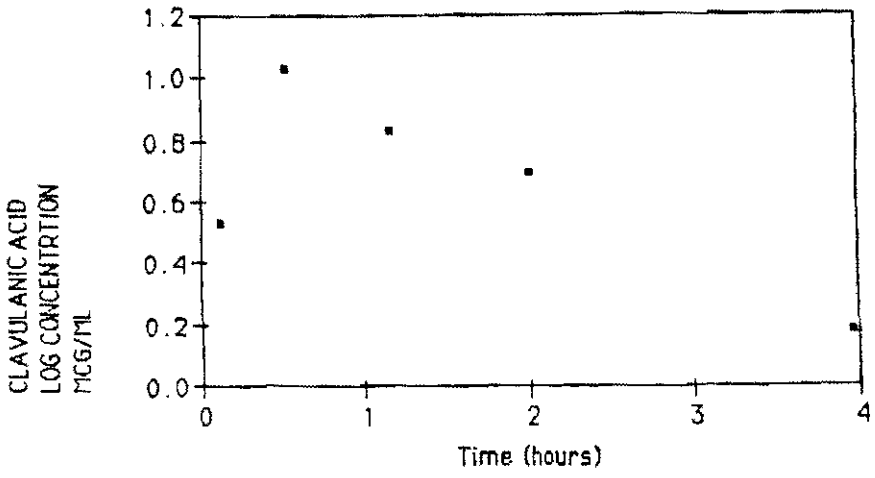
SUBJECT #4


TICARCILLIN
LOG CONCENTRATION
MCG/ML
7
6
5
4
0
1
2
3
Time (hours)

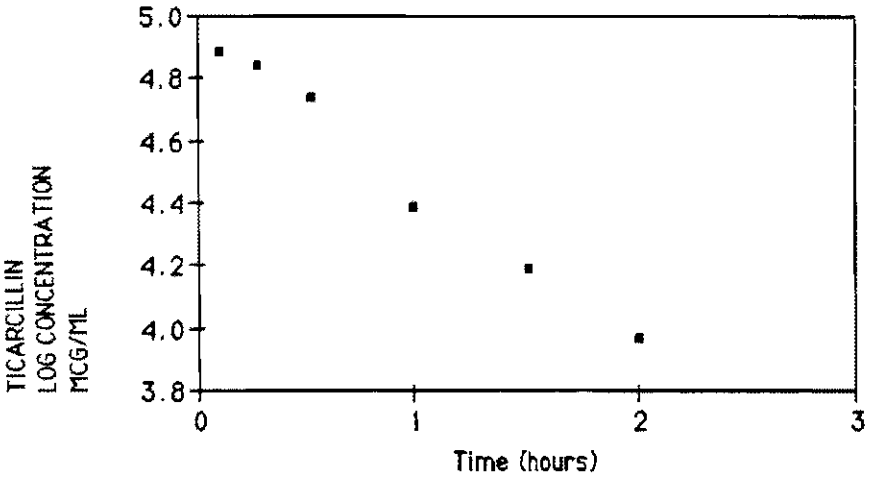

CLAVULANIC ACID
LOG CONCENTRATION
MCG/ML
3
2
1
0
-1
0
1
2
3
Time (hours)

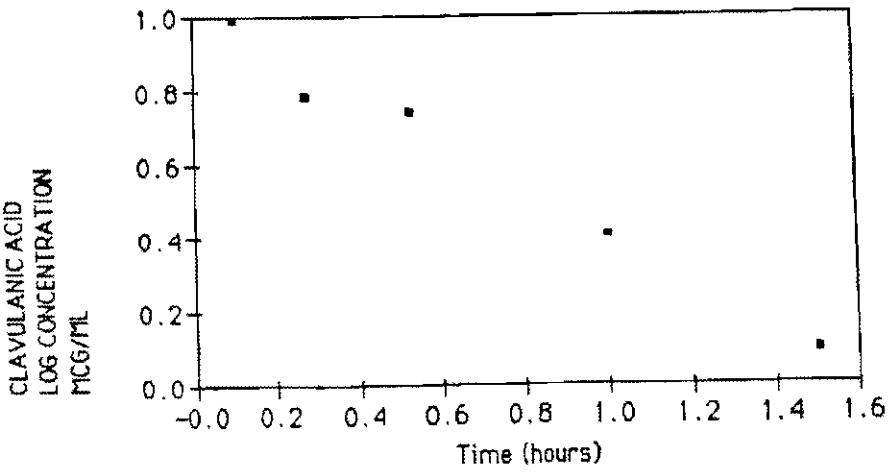
SUBJECT #5


TICARCILLIN
LOG CONCENTRATION
MCG/ML
5.2
5.1
5.0
4.9
4.8
4.7
4.6
4.5
0.0
0.5
1.0
1.5
2.0
2.5
Time (hours)

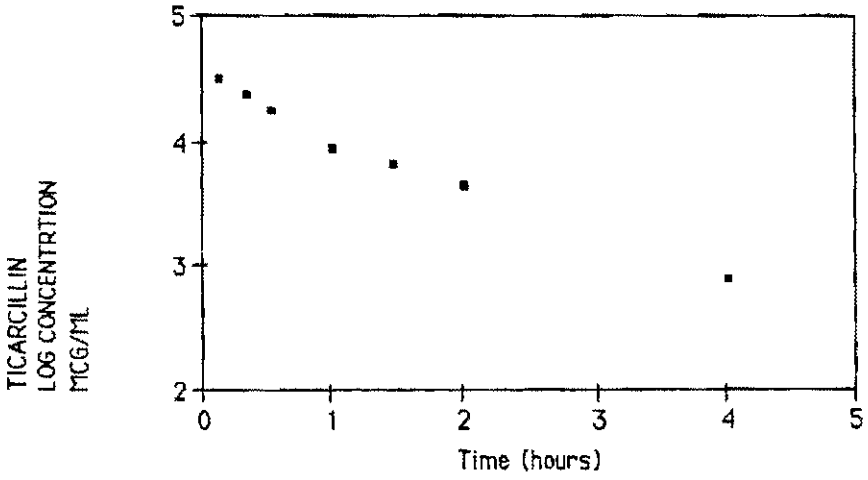

CLAVULANIC ACID
LOG CONCENTRTION
MCG/ML
1.2
1.0
0.8
0.6
0.4
0.2
0.0
0
1
2
3
4
Time (hours)

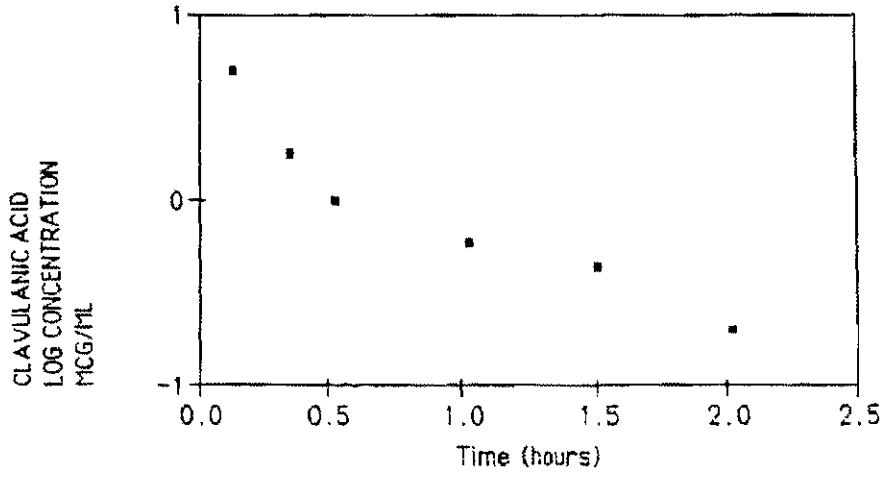
SUBJECT #7


TICARCILLIN
LOG CONCENTRATION
MCG/ML
5.0
4.8
4.6
4.4
4.2
4.0
3.8
0
1
2
3
Time (hours)

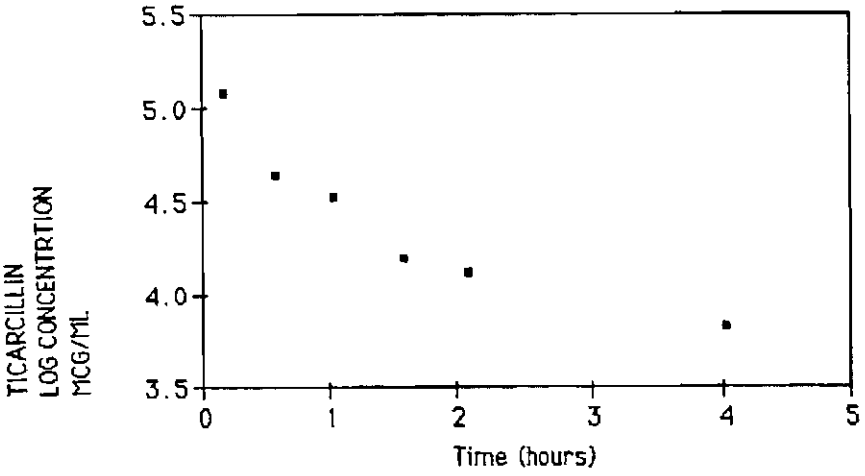

CLAVULANIC ACID
LOG CONCENTRATION
MCG/ML
1.0
0.8
0.6
0.4
0.2
0.0
-0.0
0.2
0.4
0.6
0.8
1.0
1.2
1.4
1.6
Time (hours)

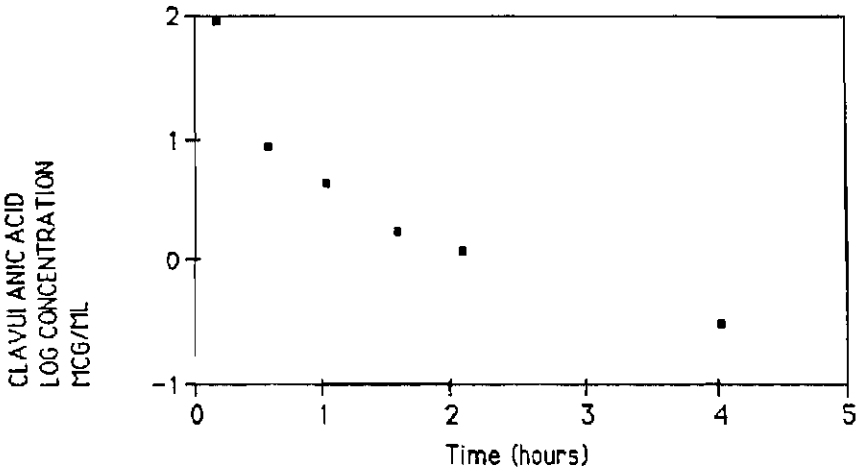
SUBJECT #8


TICARCILLIN
LOG CONCENTRTION
MCG/ML
5
4
3
2
0
1
2
3
4
5
Time (hours)


CLAVULANIC ACID
LOG CONCENTRATION
MCG/ML
1
0
-1
0.0
0.5
1.0
1.5
2.0
2.5
Time (hours)

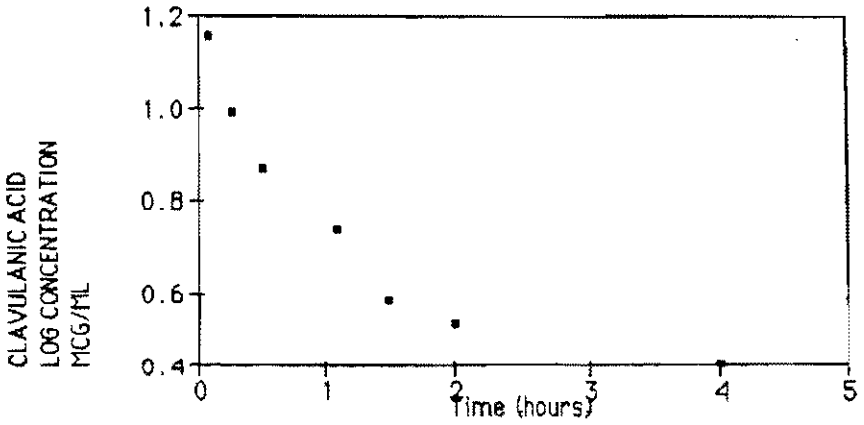
SUBJECT #9


TICARCILLIN
LOG CONCENTRTION
MCG/ML
5.5
5.0
4.5
4.0
3.5
0
1
2
3
4
5
Time (hours)

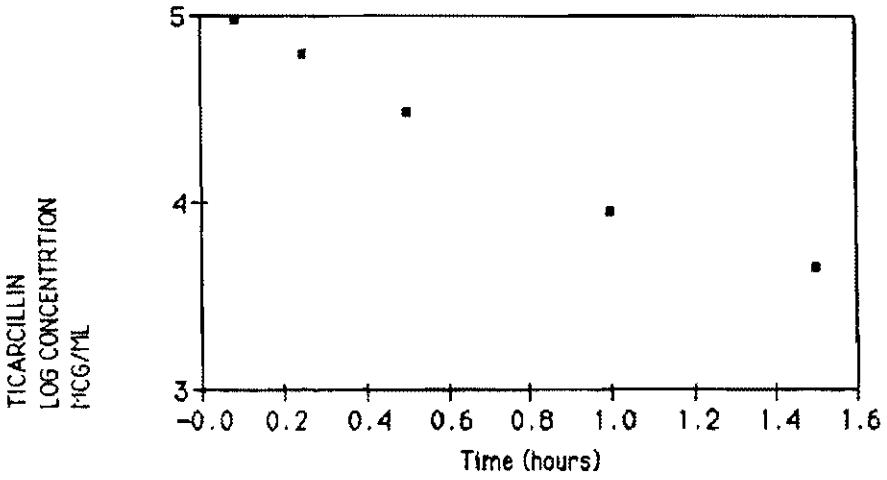

CLAVULANIC ACID
LOG CONCENTRATION
MCG/ML
2
1
0
-1
0
1
2
3
4
5
Time (hours)

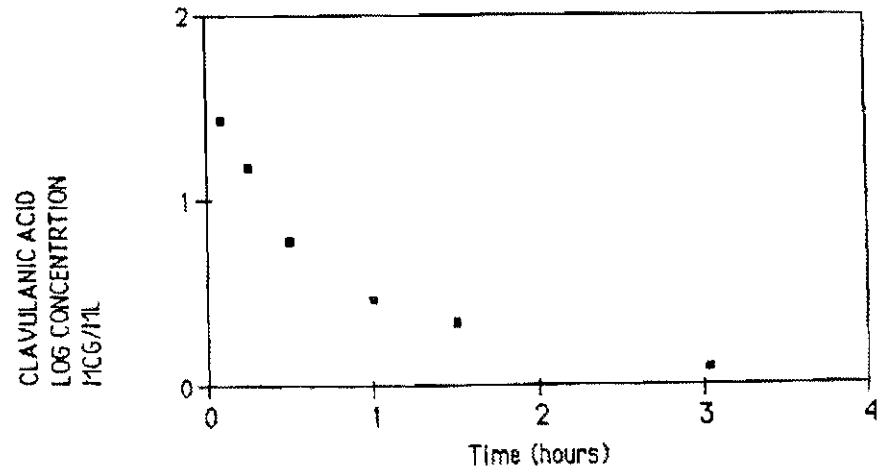
SUBJECT #10

TICARCILLIN DATA EXCLUDED

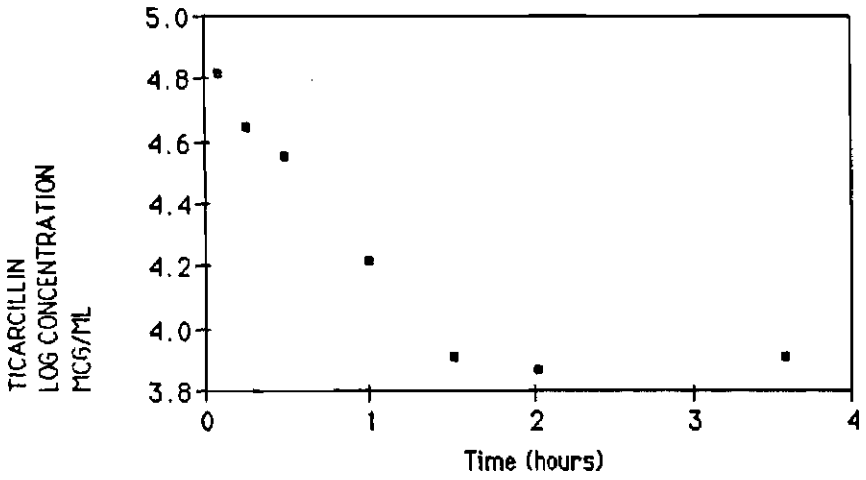


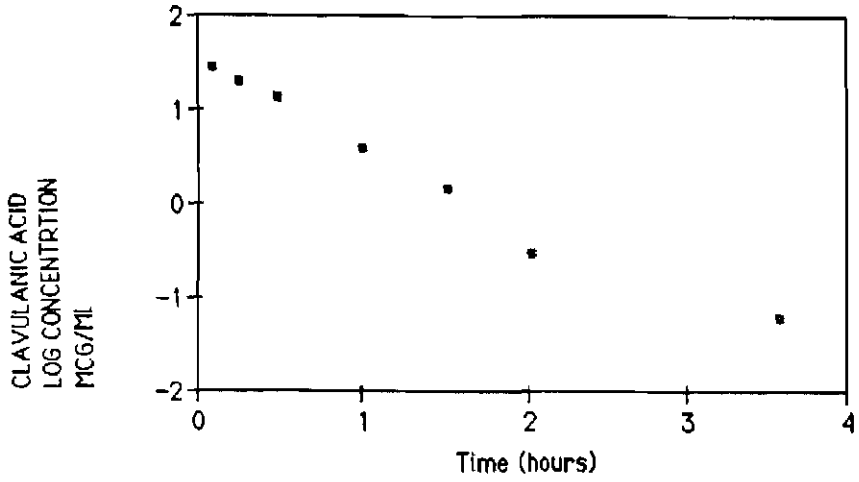
SUBJECT #11


TICARCILLIN
LOG CONCENTRTION
MCG/ML
5
4
3
-0.0
0.2
0.4
0.6
0.8
1.0
1.2
1.4
1.6
Time (hours)

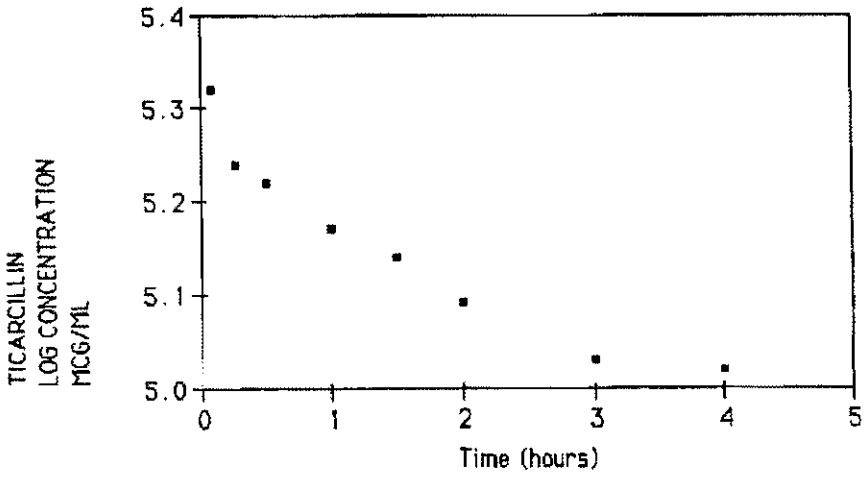

CLAVULANIC ACID
LOG CONCENTRTION
MCG/ML
2
1
0
0
1
2
3
4
Time (hours)

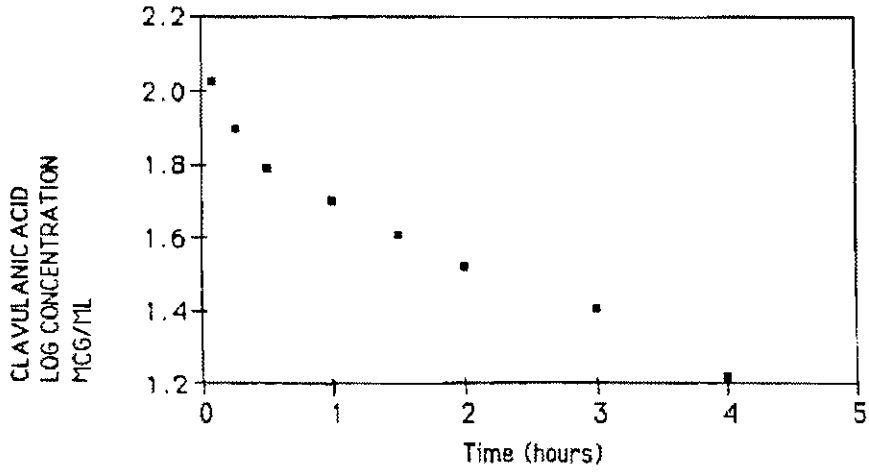
SUBJECT #12


TICARCILLIN
LOG CONCENTRATION
MCG/ML
5.0
4.8
4.6
4.4
4.2
4.0
3.8
0
1
2
3
4
Time (hours)

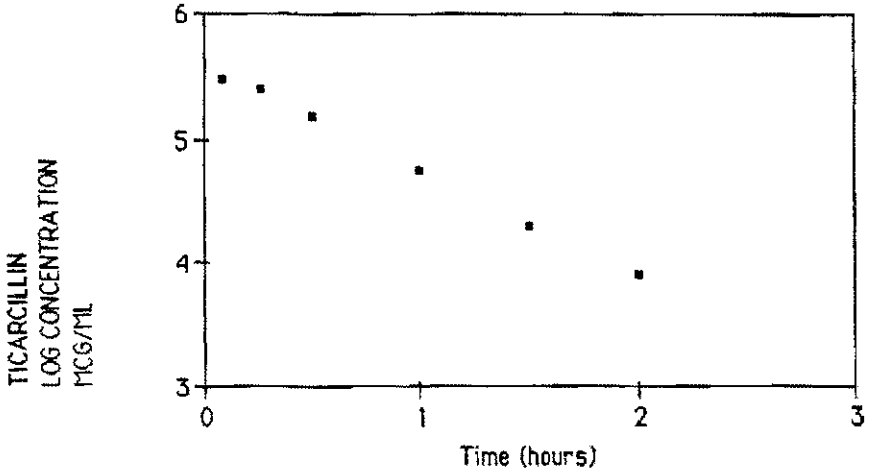

CLAVULANIC ACID
LOG CONCENTRTION
MCG/ML
2
1
0
-1
-2
0
1
2
3
4
Time (hours)

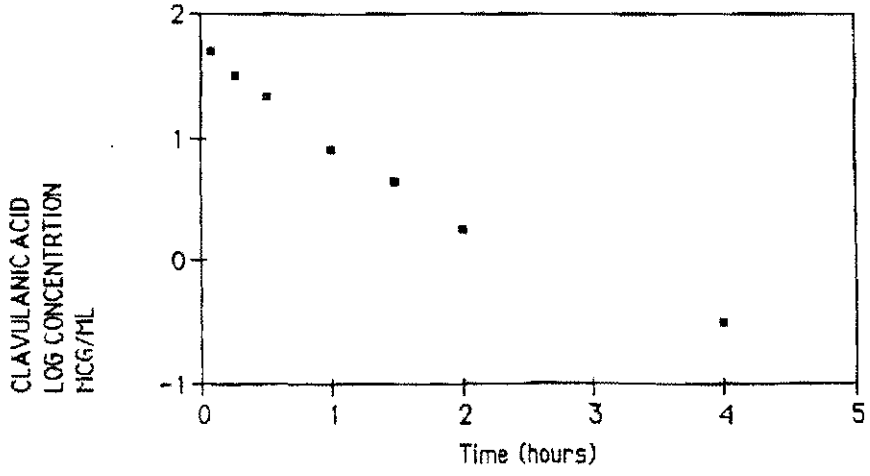
SUBJECT #13


TICARCILLIN
LOG CONCENTRATION
MCG/ML
5.4
5.3
5.2
5.1
5.0
0
1
2
3
4
5
Time (hours)

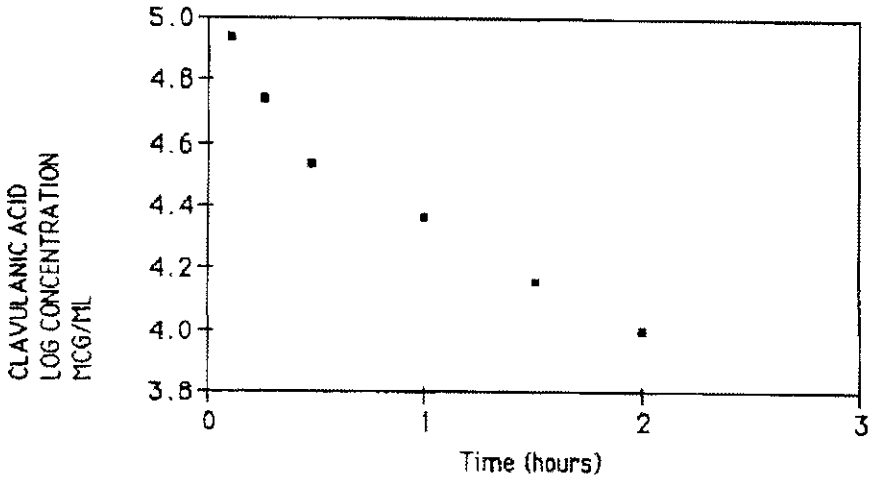

CLAVULANIC ACID
LOG CONCENTRATION
MCG/ML
2.2
2.0
1.8
1.6
1.4
1.2
0
1
2
3
4
5
Time (hours)

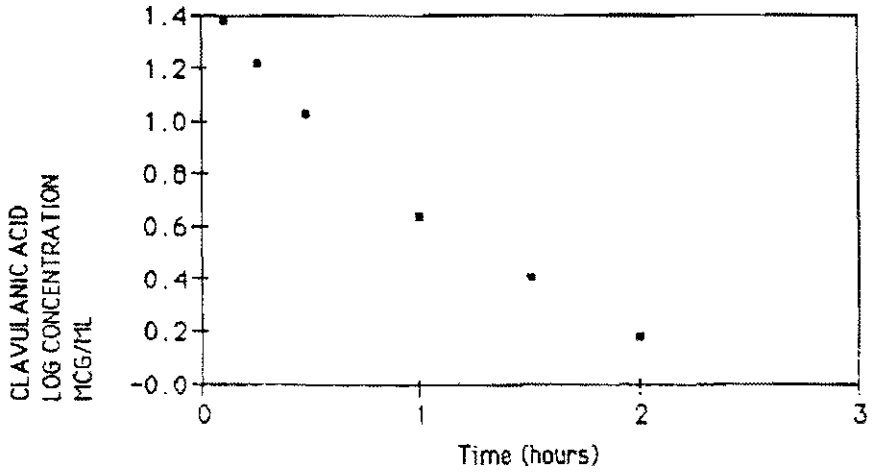
SUBJECT #14


TICARCILLIN
LOG CONCENTRATION
MCG/ML
6
5
4
3
0
1
2
3
Time (hours)


CLAVULANIC ACID
LOG CONCENTRTION
MCG/ML
2
1
0
-1
0
1
2
3
4
5
Time (hours)

SUBJECT #15


CLAVULANIC ACID
LOG CONCENTRATION
MCG/ML
5.0
4.8
4.6
4.4
4.2
4.0
3.8
0
1
2
3
Time (hours)


CLAVULANIC ACID
LOG CONCENTRATION
MCG/ML
1.4
1.2
1.0
0.8
0.6
0.4
0.2
-0.0
0
1
2
3
Time (hours)

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