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Clinical Trial of the Efficacy and Safety of Ticarcillin and Clavulanic Acid

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Forty-three hospitalized patients were treated with a new antibiotic combination containing ticarcillin plus the beta-lactamase inhibitor, clavulanic acid, in a fixed combination for intravenous use. A variety of infections were treated, including pneumonia, bacteremia, urinary tract infection, and osteomyelitis. Of 50 episodes of infection in 43 patients, 44 clinical cures were obtained, with 5 patients improving and 1 patient failing to respond to treatment. In vitro susceptibility testing of 101 clinical isolates was notable for the rarity of resistance to the combination antibiotic. Of specific interest, all 14 isolates of *Staphylococcus aureus* were susceptible to ticarcillin plus clavulanic acid, whereas only 2 of the 14 isolates were susceptible to ticarcillin alone. Adverse reactions to the study drug were minimal; eosinophilia, unaccompanied by other allergic phenomena, and oral candidiasis were most frequent. Overall, the combination of ticarcillin with the beta-lactamase inhibitor, clavulanic acid, appears to be a safe and effective drug for the treatment of infections caused by susceptible organisms.

A novel approach to antimicrobial chemotherapy is represented by the combination of the beta-lactamase inhibitor clavulanic acid and currently available ticarcillin as a fixed ratio solution for intravenous use. Clavulanic acid is a naturally occurring beta-lactamase inhibitor produced by *Streptomyces clavuligerus* (4, 18) with a structure shown to be a fused beta-lactam distinct from those of the penicillins and cephalosporins. Although clavulanic acid is a weak antimicrobial agent, it does inhibit specifically and irreversibly the beta-lactamases of Richmond classes II, III, IV, and V (15, 19). Functionally, this would indicate the probable inhibition of the beta-lactamases produced by strains of *Staphylococcus aureus*; *Escherichia coli*; members of the genera *Klebsiella*, *Proteus*, *Shigella*, and some *Pseudomonas*; and *Hemophilus influenzae*. Indeed, in vitro studies have indicated that there is effective antimicrobial activity against these organisms when clavulanic acid is combined with ticarcillin in clinically achievable concentrations (10, 16). To evaluate the efficacy and safety of this formulation, we studied 43 patients hospitalized for infections in an open test of a fixed, intravenously administered combination of ticarcillin and clavulanic acid (TiClav).

MATERIALS AND METHODS

Patient enrollment and clinical criteria. Fifty-nine patients from the Cincinnati Veterans Administration Medical Center and the University of Cincinnati Medical Center were enrolled in the study after written informed consent was obtained. Admission criteria for enrollment included signs and symptoms compatible with a bacterial infection and culture of putatively pathogenic organisms from a clinically involved site. Disease categories included lower respiratory tract infections, pneumonia, bacteremia, urinary tract infection, soft tissue infection, and bone or joint infections. In all cases, pretreatment cultures were obtained not more than 2 days before initiation of therapy. Patients who had received antibiotics within 72 h before institution of TiClav therapy were included only if susceptibility data indicated a pathogen resistant to the initial antibiotic used was present at the time the patient was admitted to the study. The following exclusionary criteria were employed: (i) history of allergy to penicillins or cephalosporins; (ii) serum creatinine concentrations chronically greater than 2.5 mg/dl; (iii) pregnancy; (iv) leukopenia (defined as leukocyte count less than 4800 cells per mm^3).

The criteria used for the diagnosis of purulent bronchitis included respiratory symptoms, fever, sputum production, and a gram-stained specimen of sputum. Pneumonia was diagnosed if a chest radiograph revealed a pulmonary infiltrate. Bronchopulmonary secretions were obtained by deep expectoration, endotracheal intubation with suction, bronchoscopy, or transtracheal aspiration. Gram-stained smears were considered reflective of lower respiratory secretions if the number of polymorphonuclear leukocytes exceeded the number of squamous epithelial cells and if organisms of a single morphological type accounted for greater than one-half of the total number of organisms seen. Urinary tract infections were defined by symptoms of fever, back pain, or dysuria plus laboratory findings of pyuria and growth of $>10^5$ organisms per ml from either clean-catch or catheter-obtained urine specimens. The diagnosis of soft tissue and bone or joint infections required appropriate symptoms plus positive culture obtained by direct closed-space aspiration of an infected cavity or subcutaneous area before treatment. Bacteremia was defined by symptoms of fever, chills, or hypotension and the isolation of a pathogenic organism from at least one pretreatment blood culture.

The following tests were performed on all patients before treatment, at 5-day intervals during therapy, and after discontinuation of TiClav: (i) complete blood count and differential count; (ii) platelet count; (iii) urinalysis; (iv) tests of hepatic and renal function, including serum levels of serum glutamic oxaloacetic transaminase, serum glutamic pyruvic transaminase, total bilirubin, alkaline phosphatase, albumin,

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blood urea nitrogen, and creatinine. The efficacy of TiClav was evaluated by both clinical and bacteriological criteria. Clinically, patients were considered to be cured if they became asymptomatic and abnormal physical findings were resolved. Clinical improvement was defined as a definitive reduction in symptoms and clinical signs but with incomplete resolution of infection. Cases were scored as clinical failures when there was no apparent response to therapy.

Patients were considered to be cured bacteriologically if the initial pathogen was eliminated during therapy and the cultures remained negative after the cessation of therapy. Bacteriological improvement was defined as clinical resolution with closure of drainage sites such that follow-up culture material was not available from areas that may have harbored living organisms without apparent disease, as in osteomyelitis. Bacteriological failure was defined as persistence of the initial pathogen during therapy, with or without resolution of clinical illness. The final results of therapy for urinary tract infections were evaluated bacteriologically by urine cultures performed 1 month after cessation of therapy. The following criteria were employed for the exclusion of TiClav recipients from evaluation: (i) treatment duration of less than 5 days, (ii) failure to follow protocol, (iii) lack of a culture-proven pathogen before treatment.

Drug administration. TiClav was supplied in 3.1-g vials, containing 3 g of ticarcillin and 0.1 g of clavulanic acid as the potassium salt. Vials containing 3 g of ticarcillin and 0.2 g of clavulanic acid were used exclusively for urinary tract infections. The contents of one vial (dissolved in 20 ml of sterile water) was added to 5% glucose in water or normal saline and infused intravenously over 20 to 30 min. The interval of administration varied from 4 to 6 h (total, 12.4 to 18.6 g of TiClav/day), depending on the severity of infection; patients weighing less than 60 kg were treated with TiClav adjusted for weight, using 310 mg/kg per day for severe infections and 207 mg/kg per day for mild to moderate infections. Nine patients weighed less than 60 kg and required a modified daily dose. Duration of therapy varied with the type of infection treated, ranging from a minimum of 5 days to a maximum of 6 weeks in three cases of severe staphylococcal disease.

Microbial sensitivity testing. Disk susceptibility testing of all isolated strains to ticarcillin alone and to TiClav was performed by the Kirby-Bauer method. The ticarcillin test disk (Beecham Laboratories, Bristol, Tenn.) contained 75 μg of ticarcillin, and organisms were considered susceptible to this agent if the zone of growth inhibition was 15 mm or more in diameter. A zone diameter of 12 to 14 mm indicated indeterminate susceptibility, whereas a diameter of 11 mm or less indicated resistance. Isolates were tested for susceptibility to TiClav with a disk containing 75 μg of ticarcillin plus 15 μg of clavulanic acid (Beecham Laboratories). No zone sizes have been established definitely for TiClav; however, in this study, the following criteria were used for isolates: susceptibility was defined as an inhibitory zone size of 17 mm or greater, indeterminate susceptibility was defined by a zone diameter of 14 to 16 mm, and resistance was defined by a zone of 13 mm or less (13).

Quality control testing for the Kirby-Bauer procedure was conducted weekly with *E. coli* (Beecham 1532) and *Pseudomonas aeruginosa* (ATCC 27853) with control zone sizes of 24 to 30 mm and 21 to 27 mm, respectively. Some isolates obtained near the end of the study were tested for TiClav susceptibility with a disk containing 75 μg of ticarcillin plus 10 μg of clavulanic acid (rather than 15 μg of clavulanic acid). Zone sizes ≥18 mm indicated susceptible organisms; zones of 12 to 17 mm indicated indeterminate susceptibility, and zone diameters ≤11 mm indicated resistance. The change of clavulanic acid concentration in the test disks produced no substantial differences in quality control parameters. MICs were determined for all organisms falling in the indeterminate category for either ticarcillin or TiClav. MICs were determined by the agar dilution method, as specified by the National Committee for Clinical Laboratory Standards (14). For the determination of MICs of TiClav, each dilution of ticarcillin was tested in the presence of 4 μg of clavulanic acid per ml. Organisms were considered to be susceptible if the MIC of ticarcillin or TiClav was ≤64 μg/ml and resistant if the MIC was ≥128 μg/ml.

RESULTS

Forty-three patients were included in the study. Sixteen additional patients entered the trial but were excluded because of a lack of a culture-proven site of infection or death before 72 h of therapy. Only one patient had received antibiotics prior to TiClav therapy. This consisted of three doses of oral ampicillin as an outpatient before the diagnosis of purulent pericarditis caused by a penicillin-resistant strain of *S. aureus*. The mean age of the evaluable patients was 62 ± 11 (standard deviation) years and the mean weight was 64.9 ± 20.0 kg (143 ± 44 pounds). Of the 43 patients studied, 39 were male because a Veteran's Administration Medical Center served as a major source of patients. A large number of associated conditions were present in this patient population, the most frequent of which were chronic obstructive pulmonary disease, diabetes mellitus, and ethanol abuse (Table 1).

Pneumonia was the most common infection observed, and 24 episodes were treated with TiClav. Bacteremia resulting either from pneumonia or urinary tract infection was the second most common form of infection (seven cases). The remaining infections included urinary tract (six cases), skin and soft tissue (five cases), purulent bronchitis (four cases), osteomyelitis caused by *S. aureus* (two cases) and group B streptococci (one case), and staphylococcal purulent pericarditis (one case).

The organism cultured most frequently from sputum and transtracheal aspirates was *Streptococcus pneumoniae* (15 isolates), which is probably related to the fact that approximately 50% of the total episodes of infections treated were pneumonias. From the urinary tract, a wide variety of organisms were cultured although *E. coli* and *P. aeruginosa*

TABLE 1. Underlying conditions in patients treated with TiClav

Associated conditions[a]	No. of patients	Percentage of total
Chronic obstructive lung disease	20	22
Diabetes mellitus	15	16
Ethanol abuse	13	14
Neoplasm	9	10
Congestive heart failure	5	6
Post cerebrovascular accident	5	6
Coronary artery disease	4	4
Peripheral vascular disease	4	4
Prostatic hypertrophy	4	4
Other[b]	13	14

[a] Each patient may have more than one underlying condition.

[b] These include three patients with dementia, three patients with elevated initial creatinine levels in serum, two patients with drug abuse, two patients posttrauma, and one patient each with gastrointestinal hemorrhage, multiple sclerosis, and peptic ulcer disease.

were the most common with eight and six isolates, respectively. Five isolates of *S. pneumoniae* and two isolates of *E. coli* were cultured from the blood cultures of seven evaluable patients with documented bacteremia.

In vitro susceptibility testing (Table 2) of the 101 isolates obtained in this study revealed only three organisms that were resistant to TiClav. Specifically, one isolate of *Klebsiella pneumonia* and one isolate of *P. aeruginosa* were found to have MICs of 256 and 128 μg/ml, respectively, to both ticarcillin alone and TiClav. Of the other gram-negative organisms, seven isolates (four *Klebsiella* sp. and three *E. coli*) were susceptible to TiClav and resistant to ticarcillin. Among the gram-positive cocci, only one isolate, *Staphylococcus hemolyticus*, was resistant to TiClav in vitro. All 14 isolates of *S. aureus* were susceptible to TiClav, with 12 of these being resistant to ticarcillin alone.

Overall data on the 50 episodes of infection studied (in 43 patients) revealed 44 clinical cures, 5 improvements, and 1 failure. Bacteriologically, there were 40 cures, 7 improvements, and 3 failures. Of the 24 patients with pneumonia, 23 were cured clinically (Table 3); the one patient not cured of pneumonia was 55 years old and was admitted with pleuritic chest pain and right middle lobe pneumonia. Sputum cultures grew *S. pneumoniae*. After 16 days of TiClav therapy (3.1 g every 6 h), a pleural effusion had developed and the right lung infiltrate persisted. The patient remained febrile, and the peripheral blood leukocytosis (15,300/mm^3) persisted with a left shift. TiClav treatment was discontinued, and the patient was treated for 10 days with penicillin, 500 mg every 6 h orally. A chest X-ray taken 20 days after cessation of penicillin therapy revealed that the infiltrate had cleared and the peripheral leukocyte count had decreased to 9,400/mm^3. Although it is difficult to be certain, this may have been a slowly resolving pneumonia that did not clear immediately on TiClav therapy.

TABLE 2. Summary of antimicrobial susceptibility testing of 101 isolates against TiClav and ticarcillin[a]

Organism (no. of isolates)	No. of isolates susceptible to:			
	Ticarcillin	TiClav	TiClav and ticarcillin	Neither TiClav nor ticarcillin
Escherichia coli (14)	0	3	11	0
Pseudomonas aeruginosa (9)	0	0	8	1
Klebsiella sp. (11)	0	4	6	1
Proteus mirabilis (6)	0	0	6	0
Acinetobacter anitratus (3)	0	0	3	0
Haemophilus influenzae (2)	0	0	2	0
Enterobacter cloacae (2)	0	0	2	0
Other gram-negative bacteria (4)[b]	0	0	4	0
Staphylococcus aureus (14)	0	12	2	0
Streptococcus pneumoniae (17)	0	0	17	0
Other streptococci (10)	0	0	10	0
Staphylococcus epidermidis (7)	0	0	7	0
Staphylococcus hemolyticus (1)	0	0	0	1
Clostridium perfringens (1)	0	0	1	0

[a] All susceptibility tests were performed by the disk diffusion (Kirby-Bauer) method. If the result was in the indeterminate range, MICs were determined (15 isolates).

[b] These organisms include one each of the following: *Citrobacter diversus*, *Enterobacter agglomerans*, *Serratia* sp., and *Pseudomonas maltophilia*.

TABLE 3. Clinical and bacteriological outcome of TiClav therapy for 43 patients[a]

Disease	No. of episodes with the following outcomes:		
	Cure	Improved	Failure
Pneumonia	23 (20)[b]	1	0
Bacteremia	7 (7)	0	0
Urinary tract infection	6 (6)	0	0
Skin and soft tissue infection	3 (2)	1	1
Purulent bronchitis	4 (4)	0	0
Bone and joint infection	0	3[c]	0
Purulent pericarditis	1 (1)	0	0

[a] Seven patients had two infections: five patients had pneumonia and bacteremia, two patients had urinary tract infection and bacteremia.

[b] Number of bacteriological cures are shown in parentheses.

[c] Three patients with osteomyelitis were clinically well at discharge; however, cure was not documented by bone biopsy.

Two patients treated for pneumonia were classified as bacteriological failures. In one 53-year-old patient with severe chronic obstructive pulmonary disease, *S. aureus* persisted in the sputum 10 days posttherapy, despite a clinical cure. In fact, staphylococci were present in the sputum in conjunction with *S. pneumoniae* before therapy and may or may not have contributed to the clinical infection in this patient. The *S. pneumoniae* was eradicated by TiClav therapy. In a 67-year-old patient with Alzheimer's disease and left lower lobe pneumonia, *K. pneumoniae* and *Proteus mirabilis* were isolated from the sputum before TiClav therapy. Despite clearing of the pulmonary infiltrate, *K. pneumoniae* persisted in the sputum after 10 days of TiClav therapy given in a dosage of 3.1 g every 4 h. Neither of these bacteriological failures, as defined by the persistance of a positive culture, was surprising because both patients had underlying diseases that would render a bacteriological cure more difficult.

All seven of the patients with bacteremia (*S. pneumoniae*, five patients; *E. coli*, two patients) were cured both clinically and bacteriologically. Six patients with urinary tract infection were treated, and all infections were resolved with bacteriological as well as clinical cures. All patients were sufficiently ill to warrant hospitalization and all had clinical evidence of urinary tract infection. One patient had a chronic indwelling Foley catheter, two had concurrent *E. coli* bacteremia, and all patients had other debilitating conditions, including diabetes mellitus, severe cardiovascular disease, and carcinoma of the prostate.

Infections of the skin and soft tissues and bone and joint spaces and cases of purulent bronchitis responded well to TiClav therapy, with clinical and bacteriological cures in most cases. A subgroup of three patients had osteomyelitis. The first patient had bone biopsy-proven *S. aureus* osteomyelitis after open reduction of a fracture of the right tibia and fibula. After six weeks of TiClav therapy (total dosage, 775 g) as well as surgical debridement, the wound healed completely without drainage. At completion of therapy (day 42), the peripheral leukocyte count was 5500, and there was clear evidence of bone (tibia) healing on X-rays. The sedimentation rate, however, remained elevated at 105 mm/h on day 40.

The second patient had osteomyelitis caused by *S. aureus* subsequent to a fracture of the left humerus. After 1 month of TiClav therapy (total dosage, 558 g), the sedimentation rate had decreased from the initial value of 95 mm/h to 30 mm/h; the peripheral leukocyte count had decreased from an initial value of 24,500 mm^3 to 9300 mm^3 after therapy and the original sinus tract had healed.

The third patient with osteomyelitis developed a drainage site in the third digit of the left hand. An X-ray revealed osteomyelitis involving the proximal interphalangeal joint and associated bone structures. Deep culture from the area yielded a pure culture of group B, beta-hemolytic streptococci. After 3 weeks of TiClav therapy (total dosage, 688 g), the sinus tract had closed, and the peripheral leukocyte count had decreased from 11,000 to 6000. Examination of the digit 5 months later revealed no clinical recurrence.

All three of the patients with osteomyelitis had improved clinically at the time of discharge. However, a long-term follow-up is needed to determine whether bacteriological cure was actually achieved. Because the ultimate bacteriological status of these patients is indeterminate, they have been categorized as achieving bacteriological improvement only.

One 64-year-old patient with purulent pericarditis caused by *S. aureus* was treated with TiClav. The patient experienced complete resolution of infection after intravenous administration of 781 g of TiClav over a 6-week period. In addition, pericardiocentesis and partial pericardectomy was performed with removal of 1000 ml of purulent fluid. This treatment success is noteworthy because the patient had longstanding myelofibrosis with peripheral leukocyte counts ranging from 3000 to 4000 mm^3. Moreover, the patient had received 20 mg of methylpredniselone before and throughout the course of TiClav therapy.

An unequivocal TiClav treatment failure occurred in a 29-year-old patient with multiple pelvic fractures and an infected urinoma that was approached by flank incision with placement of surgical drains. Bacteriological evaluation revealed that the causative organisms were *Streptococcus faecalis* and a TiClav-resistant strain of *P. aeruginosa*. After 2 days of TiClav therapy without clinical response and after receipt of the in vitro data indicating a resistant strain of *Pseudomonas*, the drug was discontinued. Therapy was initiated with piperacillin and gentamicin, and after 4 days of this regimen, the patient became afebrile and drainage from the flank decreased markedly.

In one patient with a chronic decubitus ulcer, the lesion clinically responded well to therapy, but neither eradication of the organism nor complete healing was accomplished.

Thirteen patients were infected with ticarcillin-resistant, TiClav-susceptible organisms (*S. aureus* in nine patients, *Klebsiella* sp. in two patients, *Pseudomonas* sp. in one patient, and *E. coli* in one patient). Of these, eight patients were bacteriologically cured, and three patients were noted above as improved including the two patients with staphylococcal osteomyelitis and one patient with a chronic decubitus ulcer infected by *E. coli*.

Adverse effects of TiClav. Serious reactions specifically related to TiClav administration were infrequent, although adverse effects were observed in 15 of the 59 (25.4%) patients to whom the drug was given. The most common abnormality associated with TiClav therapy was eosinophilia (total eosinophil count, >500/mm^3) in eight patients; other allergic phenomena such as drug fever, rash, or interstitial nephritis were not observed. Four patients developed oral candidiasis; in each case, the response to either cessation of TiClav therapy at the end of treatment or an oral, nonadsorbable antifungal agent was rapid and complete. A 68-year-old patient with no underlying disease became leukopenic after 9 days of therapy with 3.1 g of TiClav every 6 h for a right upper lobe pneumonia. The initial peripheral leukocyte count of 14,900/mm^3 (89% neutrophils) fell to a low of 2700/mm^3 (45% neutrophils) on day 9 of therapy. Within 4 days after cessation of TiClav therapy, the leukocyte count had returned to 5400/mm^3. Less severe neutropenia developed in a 58-year-old alcoholic patient after 4 weeks of TiClav therapy (3.1 gm every 4 h) for streptococcal osteomyelitis. The leukocyte count of 11,000/mm^3 (85% neutrophils) obtained on admission fell to a low of 4500/mm^3 (40% neutrophils) by day 28 of therapy. Despite continued drug administration, the leukocyte count improved over the next 2 weeks to 6000/mm^3 (39% neutrophils).

Of the 59 patients, 2 experienced inflammation at the site of intravenous TiClav administration; in one patient, the intravenous catheter had remained in place for more than 72 h. Removal of the intravenous line resulted in prompt resolution in both cases.

Elevation of the potassium level in serum to 6.1 and 6.5 mEq/liter was detected in one 68-year-old patient on days 7 and 8, respectively, of TiClav therapy (3.1 g every 6 h) for an uncomplicated pneumococcal pneumonia. Concentrations of potassium in serum measured on admission and days 2 and 3 of TiClav treatment ranged from 3.1 to 4.4 mEq/liter. Within 48 h after discontinuation of TiClav therapy and administration of kayexelate resin, potassium levels in serum returned to the normal range. The creatinine concentration in serum measured on multiple occasions during and subsequent to TiClav therapy ranged from 0.5 to 1.3 mg/dl. Serial determinations of creatinine clearance yielded calculated values ranging from 40 to 48 ml/min. Other studies included the simultaneous determination of potassium levels in plasma (5.6 mEq/liter) and platelet count in plasma of 580,000/mm^3, assay of the aldosterone level in serum (5.2 ng/dl; normal value, 5 to 15 ng/dl), and assay of the stimulated cortisol level in serum (64.6 μg/dl, with baseline concentration of 18.8 μg/dl). Thus, the cause of hyperkalemia in this patient is unclear; however, the temporal association with TiClav administration is strong.

DISCUSSION

Of 50 episodes of infection treated with TiClav, 44 were cured clinically, 5 improved, and only 1 failed because of resistance of the infecting *P. aeruginosa* to the drug used in the study (Table 3). Pneumonia was the most common disease treated, accounting for 24 of the 50 episodes of infection. Of these pneumonias, the majority (17) were caused by *S. pneumoniae*, a pathogen for which a good therapeutic response is expected. However, TiClav therapy also was successful in the treatment of staphylococcal osteomyelitis and purulent pericarditis, as well as pneumonias caused by gram-negative bacilli.

Very good results also were achieved as assessed by bacteriological criteria. Excluding three patients with osteomyelitis, in whom bacteriological cure could not be proved definitively, infections were considered to be unresolved bacteriologically in only five patients. In two cases, persistence of a pathogenic organism was related to the presence of a chronic underlying disease, such as a decubitus ulcer, and in two patients with pneumonia, the pretreatment organism persisted in sputum post-drug administration, despite clinical cure or improvement. In one patient, a TiClav-resistant *Pseudomonas* strain persisted in concordance with the clinical treatment failure of an infected urinoma.

In the present study, susceptibility testing with TiClav revealed that very few of the 101 isolates were resistant to the drug (Table 2). No organisms were resistant to TiClav that were susceptible to ticarcillin. Of particular interest were the in vitro susceptibility tests of *S. aureus*; all 14

isolates of staphylococci were susceptible to TiClav, whereas only 2 of the 14 were susceptible to ticarcillin alone. Similar effectiveness of the TiClav combination in vitro as compared with ticarcillin alone was observed against *E. coli*; 3 of 14 isolates were susceptible to TiClav but not to ticarcillin. Noteworthy, however, is the single *P. aeruginosa* strain that was resistant to TiClav, perhaps related to the limited effectiveness of clavulanic acid against class 1 beta-lactamases.

The combination of each of several different penicillins with clavulanic acid has been shown to act synergistically against a wide variety of beta-lactamase-producing organisms including *S. aureus*, most members of the family *Enterobacteriaceae*, most strains of *Bacteroides fragilis*, and some strains of *Haemophilis influenzae* (1, 5, 7–12, 15, 16, 18, 20, 23). Specifically, beta-lactamase activity associated with gram-negative bacteria is irreversibly, competitively inhibited by clavulanic acid; this activity however is dependent on the class of beta-lactamase produced by the organism (15, 19). Those bacteria that possess a class I beta-lactamase, such as *P. aeruginosa* and *Serratia marcescens* are less likely to be killed by the combination of a semisynthetic penicillin and clavulanic acid (15, 17, 22).

The clinical problem posed by organisms containing a class I beta-lactamase is underscored in our study by the failure of TiClav therapy in a patient with a perinephric abscess caused by a *P. aeruginosa* that was resistant to TiClav. However, with this exception, treatment of infections by gram-negative bacilli in the present study was successful clinically in all cases in which an anatomic defect, such as a large decubitus ulcer, was not a complicating factor. Additional studies are needed to determine the clinical efficacy of TiClav as therapy for severe disease caused by *Pseudomonas* strains.

In contradistinction to the irreversible, competitive inhibition of beta-lactamases produced by gram-negative bacilli, clavulanic acid reversibly inhibits the beta-lactamase activity associated with *S. aureus* (18). As yet, however, the clinical implications of this difference in activity are not known. In our study of a variety of staphylococcal infections treated with TiClav, including osteomyelitis and purulent pericarditis, this biochemical phenomenon appeared to have no appreciable effect on the outcome because both the clinical and bacteriological responses to treatment were excellent.

Similar findings have been reported by others (2, 3, 9, 21) in both animal models and human infections with *S. aureus*. For example, the combination of ampicillin plus a beta-lactamase inhibitor, CP-45,899, is reported to be as effective as nafcillin alone in the treatment of experimental endocarditis induced by a nafcillin-susceptible strain of *S. aureus* (21). Likewise, a combination of penicillin-clavulanic acid appears to provide effective therapy in a mouse model of staphylococcal renal infection, even when the infection is caused by a penicillinase-producing *S. aureus* (9). In a recent study of 20 patients with osteomyelitis documented by bone biopsy culture, TiClav was found to be effective in 15 of the 20 patients, with "cure" documented by repeat bone biopsy after therapy. Although several organisms were cultured from the pretreatment biopsy specimens, *S. aureus* was the most common pathogen, comprising 34% of the total (V. Macko, R. Lind, B. Zeluff, and L. Gentry, Program Abstr. Intersci. Conf. Antimicrob. Agents Chemother. 23rd, Las Vegas, Nev., abstr. no. 846, 1983).

The primary adverse reaction associated with TiClav administration in this study was secondary oral candidiasis that occurred in four patients. Each of these patients was treated successfully with either a nonadsorbable antifungal agent or discontinuation of the antibiotic at the end of therapy. Neutropenia, requiring cessation of TiClav therapy, occurred in one patient (neutrophil count, 1215/mm^3). This type of adverse reaction has been observed with many penicillins and may well be related to the ticarcillin component of TiClav. Eosinophilia (count > 500/mm^3) occurred in eight patients. However, the clinical relevance of this finding is unclear because none of these individuals experienced clinical manifestations of allergy such as rash, fever, or nephritis. The infrequency of serious allergic reactions related to TiClav therapy may in part be due to the exclusion from the study of all patients with a history of any type of penicillin allergy. Intravenous catheter site inflammation was seen only in two patients despite several courses of therapy of 6 weeks duration. These adverse reactions are consistent with those seen by others using a combination of different semisynthetic penicillins and beta-lactamase inhibitors (6).

One patient developed unexplained hyperkalemia during TiClav administration. This patient was evaluated for both endocrine and metabolic disorders, yet no cause for the hyperkalemia could be found. This episode underscores the fact that TiClav contains clavulanic acid as the potassium clavulanate salt, yielding 0.4 mEq of potassium per reconstituted 3.1-g vial. Although administration of 1.6 mEq of potassium per day to this patient in conjunction with TiClav should not have presented clinical difficulties, further testing in a large number of patients will be necessary before it can be determined whether TiClav-associated hyperkalemia is more than an isolated, rare event. Overall, however, the administration of TiClav appears to be safe if accompanied by monitoring for potential hematological and electrolyte abnormalities.

In conclusion, we studied 43 patients with 50 episodes of serious infection and found TiClav to be both effective and safe in the treatment of diseases caused by susceptible gram-negative and gram-positive organisms. Further studies will be required to evaluate the comparative efficacy of TiClav with penicillin G or the antistaphylococcal penicillins in infections caused by organisms also susceptible to these antibiotics.

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