Antimicrobial activity of ceftriaxone compared with cefotaxime in the presence of serum albumin

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SK NATH, GA FOSTER, LA MANDELL, C ROTSTEIN. Antimicrobial activity of ceftriaxone compared with cefotaxime in the presence of serum albumin. Can J Infect Dis 1995;6(1):21-27. The effect of serum albumin on the antimicrobial activity of ceftriaxone, cefotaxime, and a 1:1 ratio of cefotaxime and its desacetyl metabolite against nonpseudomonal Gram-negative bacilli was determined. Antimicrobial activity of drugs was evaluated by measuring minimum inhibitory (MIC) and bactericidal (MBC) concentrations in broth with and without human serum albumin. The analysis of logarithmically transformed mean MICs and MBCs showed that there was a highly significant interaction between drug and serum albumin (P<0.0001). The inhibitory and bactericidal activities were greatest for cefotaxime followed by cefotaxime/desacetylcefotaxime and ceftriaxone (P<0.01). Time-kill kinetics demonstrated that ceftriaxone was less bactericidal than cefotaxime in broth with albumin. On the basis of these results it was concluded that the in vitro antimicrobial activity of ceftriaxone compared with that of cefotaxime was significantly diminished in the presence of serum albumin.

Key Words: Antimicrobial activity, Cefotaxime, Ceftriaxone, Serum albumin

Activité antimicrobienne du ceftriaxone comparée à celle du céfotaxime en présence d'albumine sérique

RÉSUMÉ : L'effet de l'albumine sérique sur l'activité antimicrobienne du ceftriaxone, du céfotaxime et d'un ratio 1:1 de céfotaxime et de son métabolite désacétyle contre des bacilles gram négatifs autres que Pseudomonas a été évalué. L'activité antimicrobienne des médicaments a été mesurée à l'aide des concentrations minimales inhibitrices (CMI) et des concentrations bactéricides dans un bouillon de culture avec ou sans albumine sérique humaine. L'analyse des moyennes de CMI et des concentrations bactéricides transformées logarithmiquement a révélé une interaction très significative entre le médicament et l'albumine sérique (P<0,0001). Les activités inhibitrices et bactéricides ont été les plus importantes pour le céfotaxime suivi du céfotaxime/désacétyle céfotaxime et du ceftriaxone (P<0,01). La chronocinétique a démontré que le ceftriaxone était moins bactéricide que le céfotaxime dans le bouillon renfermant de l'albumine. Sur la base de ces résultats, il a été conclu que l'activité antimicrobienne in vitro du ceftriaxone était nettement moindre en présence d'albumine du sérum en comparaison avec celle du céfotaxime.

THIRD-GENERATION CEPHALOSPORINS ARE OFTEN USED IN the therapy of serious nosocomial Gram-negative bacterial infections. Ceftriaxone and cefotaxime are similar in antibacterial spectrum and resistance to beta-lactamases, but differ markedly in serum protein binding and elimination half-life (ceftriaxone: 95% protein bound, elimination half-life of 8.8 h versus cefotaxime: 35%, 1.2 h) (1,2). It has been suggested that serum protein binding may diminish therapeutic efficacy by affecting antibacterial activity and drug distribution (3). Thus, high serum protein binding of ceftriaxone may in fact limit its in vitro activity (4) and impair its therapeutic efficacy compared with that of cefotaxime (5).

In the present investigation, using statistical methods we evaluated differences in the inhibitory and bactericidal activities of ceftriaxone, cefotaxime, and 1:1 combination of cefotaxime and its metabolite desacetylcefotaxime against 121 clinical isolates of nonpseudomonal Gram-negative bacilli in the presence of human serum albumin. Using a time-kill kinetic method we also assessed the diminished killing of organisms by ceftriaxone compared with that of cefotaxime in broth with albumin.

MATERIALS AND METHODS

One hundred and twenty-one bacteremic isolates of nonpseudomonal Gram-negative bacilli (77 *Escherichia coli*, 18 *Klebsiella pneumoniae*, four *Klebsiella oxytoca*, five *Proteus mirabilis*, four *Citrobacter freundii*, nine *Enterobacter cloacae* and four *Enterobacter aerogenes*) were used. The isolates were from a stock culture collection, and antimicrobial sensitivities were determined using the MicroScan system (Travenol Laboratories, New Jersey) with break point minimum inhibitory concentration (MICs) in the susceptible category (less than 8 μg/mL) for both ceftriaxone and cefotaxime. Six other nonpseudomonal Gram-negative bacterial strains (two *E coli*, two *E cloacae* and two *K pneumoniae*) isolated from blood and sputum of patients with pneumonia in an intensive care unit were employed in the study of killing kinetics in broth only and in broth containing 48% and 95% equivalent levels of human serum albumin.

Cation-adjusted Mueller-Hinton Broth (CAMHB) (Difco Canada [Lot No G3DXRS]) and nutrient agar (Becton Dickinson BBL Canada [Lot No E4DYYC]) were employed. For each medium, a single batch was used for all in vitro testing.

The antibiotic standard powders employed in the study and their suppliers were: ceftriaxone (Hoffmann-La Roche Ltd [Lot No 12592]); cefotaxime (Hoechst-Roussel Inc [Lot No 112009]); and desacetylcefotaxime (Hoechst-Roussel Inc [Lot No 8A0203B]).

MICs for the organisms were determined by the broth microdilution method (6). Antibiotic stock solutions were prepared according to the manufacturer's instructions. Ceftriaxone, cefotaxime and the 1:1 combination of cefotaxime with its desacetyl metabolite were tested in broth with and without serum albumin using serial doubling dilutions of each antibiotic (0.015 to 8 mg/L). Broth with serum albumin contained 19 g/L (for time-kill kinetics only) and 38 g/L albumin, equivalent to 48% and 95% (weight/volume) albumin in

TABLE 1
Susceptibility of nonpseudomonal Gram-negative bacilli (n=121) to ceftriaxone (CAX), cefotaxime (CFT) and cefotaxime/desacetylcefotaxime (1:1; CFT/DACT) in broth only (0%) and broth with 95% equivalent human serum albumin

Albumin concentration (%)	CAX	CFT	CFT/DACT
MIC (mg/L): MIC$_{90}$			
0	0.125	0.250	0.500
95	1.000	0.250	0.500
MBC (mg/L): MBC$_{90}$			
0	0.250	0.500	1.000
95	2.000	1.000	1.000

MBC Minimum bactericidal concentration; MIC Minimum inhibitory concentration

normal human serum. The serum albumin was obtained from blood collected from healthy volunteer donors by the Blood Services of the Canadian Red Cross Society (manufactured and distributed as 25% solution, USP 100 mL by Miles Canada Inc). A single batch of serum albumin was used for all in vitro testing. All strains grew in the serum albumin and were included in this study. The drug concentration that finally inhibited growth without any amount of visible growth at higher concentrations was recorded as the MIC after incubation of the panels for 18 h at 35°C. Quality control tests were conducted by including *E coli* ATCC 25922 in each batch of tests. MICs for ceftriaxone and cefotaxime were always found to be within the acceptable ranges.

For minimum bactericidal concentration (MBC) determinations, duplicate 0.01 mL samples were removed from each well without growth and dispensed by spreading across the surface of nutrient agar plates. Results were recorded after incubation of plates for 18 h at 35°C. The initial inocula were determined and ranged from 3 to 4×10^5 colony-forming units (cfu)/mL. The MBC was defined as the lowest concentration producing at least 99.9% killing of the original inoculum, using the appropriate rejection values described by Pearson et al (7).

Bactericidal activity of ceftriaxone and cefotaxime against six nonpseudomonal Gram-negative bacteria was also measured using the time-kill kinetic method (8). The antibiotic concentrations that were used represented the MBC for each strain tested. Inoculated broths containing approximately 3.5×10^5 cfu/mL and antibiotic were incubated, and at 0, 1, 2, 4, 6, 18 and 24 h intervals, a 0.01 mL aliquot was removed from each of the sample tubes and serially diluted (1:10). A 0.1 mL of diluent was plated on nutrient agar. Viable counts were determined after incubation of the plates for 18 h at 35°C. The bacterial survival measured as $\log_{10}$ cfu was plotted against time (hours). A time-kill curve was established for each strain. The negative effect of serum albumin on bacterial killing was assessed by a $2\log_{10}$ or greater increase in cfu (100-fold decrease in killing) at 6 h instead of 24 h for the convenience of plotting and extrapolation.

For data analyses, MIC and MBC results less than 0.015 and greater than 8 mg/L were converted to 0.007 and 16
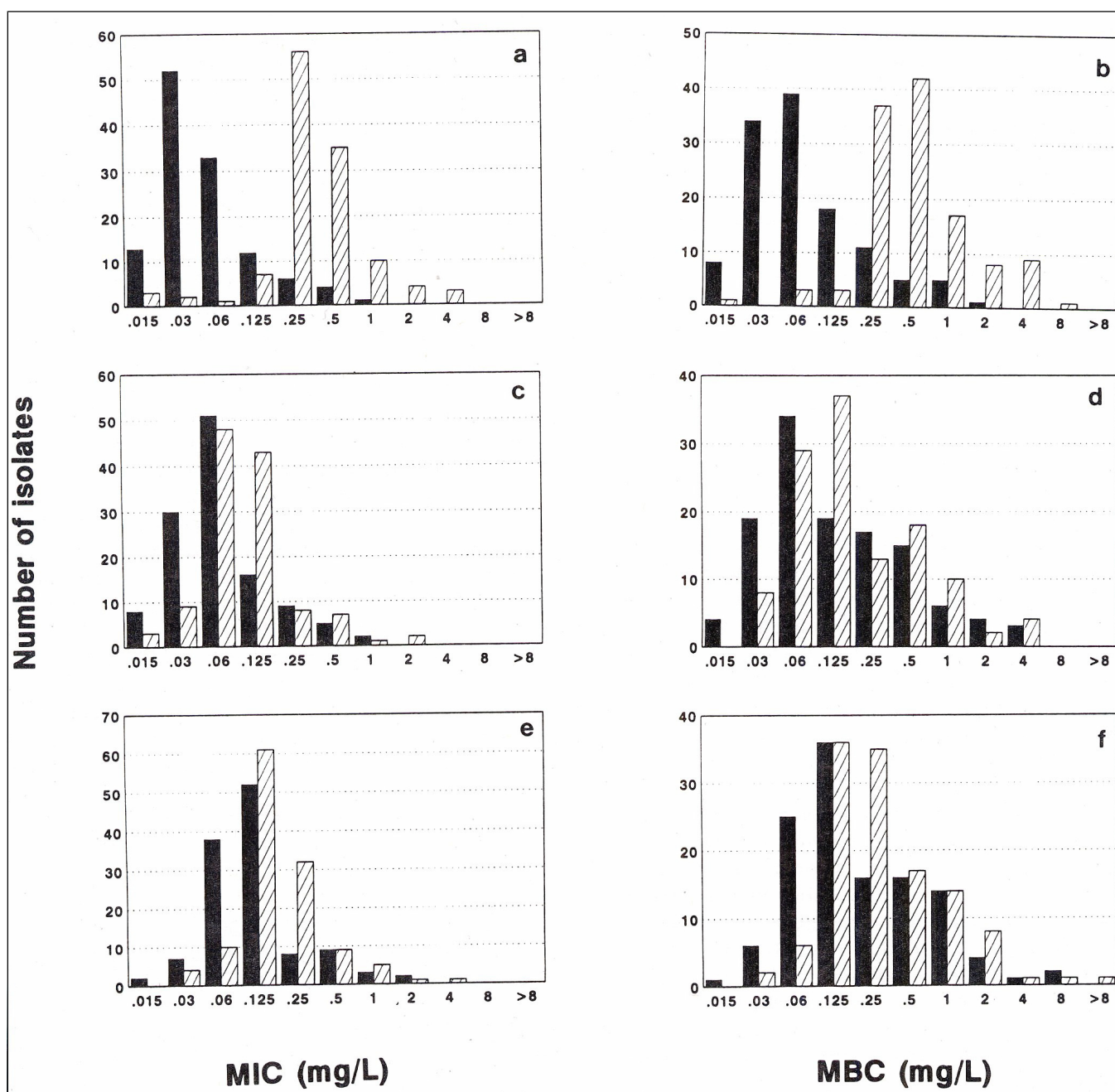
Figure 1) *Frequency distribution of minimum inhibitory concentrations (MICs) and minimum bactericidal concentrations (MBCs) (mg/L). All organisms were tested against ceftriaxone (MIC, MBC; a, b), cefotaxime (MIC, MBC; c, d), and cefotaxime/desacetylcefotaxime (MIC, MBC; e, f). Solid bars: in vitro testing in broth without serum albumin; hatched bars: in vitro testing in broth with 95% equivalent serum albumin*

mg/L. Parametric tests were used to test for differences among the means of the natural logarithmic transformed measurements (ie, geometric means). Two-way analysis of variance (ANOVA) was used to determine whether there was an interaction between antibiotic and serum albumin concentration. One-way ANOVA was used to determine whether there were differences among antibiotics at each of the serum albumin concentrations. When differences occurred, the Scheffé post-hoc test indicated which mean(s) differed significantly from the others.

RESULTS

The susceptibility data of the bacterial strains in broth and broth with serum albumin are shown in Table 1. A marked effect of serum albumin on the MIC_{90} and MBC_{90} was noted. The ceftriaxone MIC_{90} and MBC_{90} increased eightfold in the presence of serum albumin. The MIC_{90} of cefotaxime and cefotaxime/desacetylcefotaxime were virtually unaffected by the addition of serum albumin. There were minor differences in the MBC_{90} of cefotaxime and cefotaxime/desacetylcefotaxime in broth compared with broth with serum albumin.

TABLE 2
Statistical analysis of raw data of minimum inhibitory concentrations (MICs) and minimum bactericidal concentrations (MBCs) of ceftriaxone (CAX), cefotaxime (CFT) and cefotaxime/desacetylcefotaxime (1:1; CFT/DACT) in broth only (0%) and broth with 95% equivalent human serum albumin

Albumin concentration (%)	Geometric mean			P value*
	CAX	CFT	CFT/DACT	
MIC (mg/L)				
0	0.045	0.063	0.112	0.05
95	0.336	0.095	0.169	0.0001
MBC (mg/L)				
0	0.072	0.126	0.199	0.05
95	0.533	0.183	0.291	0.0001

Based on the one-way analysis of variance

The frequency (number) distribution for the organisms inhibited (MIC) or killed (MBC) at the antibiotic concentrations are shown in Figure 1. For cefotaxime and cefotaxime/desacetylcefotaxime, the majority of the MIC results were clustered at the three drug concentrations (Figure 1c,e). For ceftriaxone MICs (Figure 1a), the isolates were distributed over two clusters (0.03 to 0.06 mg/L in absence of albumin and 0.25 to 0.5 mg/L in presence of albumin). Similar differences are observed for the MBC results of cefotaxime and cefotaxime/desacetylcefotaxime versus ceftriaxone (Figure 1d,f versus 1b). Since the distributions of MIC and MBC raw data were highly skewed, statistical analyses were performed on the geometric means. Two-way ANOVA of MICs and MBCs showed that there was a highly significant interaction between drug and serum albumin (P<0.0001). The extent of this effect was evaluated by one-way ANOVA of MICs tested with the Scheffé post-hoc comparison. There were significant differences in geometric mean MICs and MBCs among the three drugs in broth only (P=0.05) and broth with 95% equivalent serum albumin (P=0.0001) (Table 2). The one-way ANOVA of MICs with the Scheffé post-hoc comparison definitively showed that cefotaxime and cefotaxime/ desaceytlcefotaxime were significantly more active than ceftriaxone when tested with albumin (P<0.01). Cefotaxime was found to be significantly more inhibitory than a 1:1 combination of cefotaxime and its desacetyl metabolite in broth without and with albumin (P<0.01). Even when serum albumin was added, cefotaxime had the most potent bactericidal activity (P<0.01).

The effects of serum albumin on the bactericidal activity of ceftriaxone and cefotaxime were also assessed by the time-kill kinetic analysis. Any reduction in bactericidal activity was assessed by determination of the survival rate ($\log_{10}$ cfu/mL versus time [hours]) of bacteria when exposed to a drug in broth containing 48% and 95% equivalent concentrations of serum albumin. Six strains with elevated MBCs of ceftriaxone were tested: two *E coli* strains (Figure 2a,b) with ceftriaxone MBCs of 0.03 and 0.125 mg/L that increased to 0.5 and 2.0 mg/L, respectively, by addition of serum albumin; two *E cloacae* strains (Figure 2c,d) with ceftriaxone MBCs of 0.5 and 0.25 mg/L that rose to 2.0 mg/L in broth with serum albumin; and

two *K pneumoniae* strains (Figure 2e,f) with ceftriaxone MBCs of 0.06 and 0.125 mg/L that increased to 0.5 and 4.0 mg/L in serum albumin. Only one *K pneumoniae* strain tested (Figure 2f) had an elevation in cefotaxime MBC (0.03 to 1.0 mg/L). Serum albumin at 48% or 95% equivalent serum levels did not overtly affect the bactericidal activity of cefotaxime based on $2\log_{10}$ or greater increase in survival (cfu/mL) of bacteria at 6 h or 24 h. In contrast, a marked negative effect on the bactericidal activity of ceftriaxone was demonstrated for all six strains with the 95% equivalent serum albumin concentration and for four strains at the 48% equivalent concentration. There was no difference in the extent of killing at 6 h or 24 h, when the bactericidal activity of the antibiotics was compared in the presence of 48% or 95% equivalent serum albumin.

DISCUSSION

The relationships between serum protein binding and the distribution of beta-lactam antibiotics has been extensively studied and reviewed over the past two decades (9-19). The differences in serum protein binding between ceftriaxone and cefotaxime have been established (1,2). Methodology has been developed to compare the pharmacokinetics of antibiotics that differ in protein binding (20). Protein binding may be of importance in antibacterial chemotherapy because the bound antibiotic is essentially unavailable for antibacterial activity (14,21). This effect should be reflected by an increase in MIC and MBC under the influence of serum protein. The present study was not intended to quantify the total and free concentrations of ceftriaxone and cefotaxime in serum (1,2,19), but rather to evaluate the change in in vitro inhibitory and, more important, bactericidal activity of ceftriaxone, cefotaxime and cefotaxime/desacetylcefotaxime (in 1:1 combination) against 121 nonpseudomonal Gram-negative bacteria in the presence of human serum protein. Since ceftriaxone is predominantly bound to albumin (22), the present investigation employed 48% and 95% equivalent levels (19 and 38 gm/L) of human serum albumin, instead of diluting with 25% or 50% (volume/volume) of human serum as described by Jones and Barry (4).

We found that MIC90 (1 mg/L) and MBC90 (2 mg/L) for ceftriaxone in the presence of 95% equivalent serum albumin increased eightfold and were at least a twofold dilution lower than those of cefotaxime (0.25 and 1 mg/L) and cefotaxime/desacetylcefotaxime (0.5 and 1 mg/L), respectively. Because the MIC90, a frequently used percentile to evaluate in vitro activity, is prone to error, even in symmetrical data distributions (23,24), and with nonsymmetrical or skewed distributions one should be cautious of using any percentile as an estimator of in vitro activity. We employed the natural logarithmic transformed measurements (ie, geometric means) of MICs and MBCs to achieve a more accurate measure of central tendency (23,24). The geometric mean MIC and MBC were the lowest for ceftriaxone indicating it had the best antimicrobial activity in broth only. However, based on the geometric means, activity of cefotaxime was superior in broth with serum albumin.

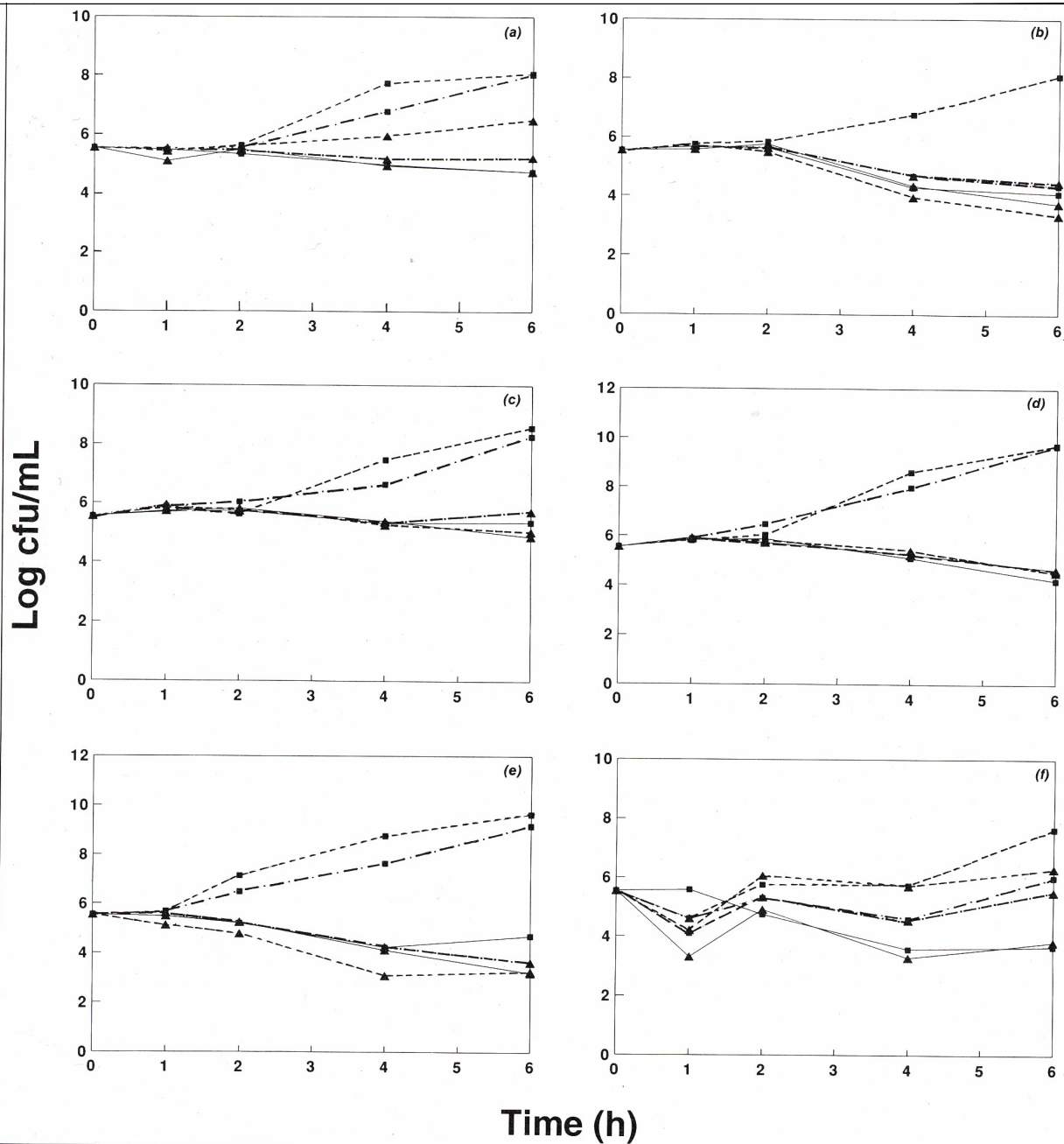Highly significant elevations in the geometric mean MICs

Figure 2) *Killing curves for six selected strains of nonpseudomonal Gram-negative bacilli at an inoculum 3.5x10⁵ colony-forming units (cfu)/mL. The antibiotic concentrations used were equal to the minimum bacterial concentrations in broth. Two* Escherichia coli *(a,b); two* Enterobacter cloacae *(c,d); and two* Klebsiella pneumoniae *(e,f) strains were tested.* —■— *Ceftriaxone without albumin,* –·–■–·– *ceftriaxone with 48% equivalent serum albumin, and* ---■--- *Ceftriaxone with 95% equivalent serum albumin;* —▲— *Cefotaxime without serum albumin,* –·–▲–·– *cefotaxime with 48% albumin, and* ---▲--- *cefotaxime with 95% albumin*

and MBCs of ceftriaxone were observed by two-way ANOVA when in vitro testing was switched from 0% (broth only) to 95% equivalent serum albumin. There were also marked differences between cefotaxime and cefotaxime/desacetylcefotaxime. Cefotaxime proved more active than the 1:1 combination of cefotaxime and its metabolite, although an earlier report documented the advantages of antimicrobial agents that have active metabolites (25). Mandell and Afnan (26) also reported synergistic activity of desacetylcefotaxime

and its parent compound in the presence of neutrophils. The one-way ANOVA of geometric mean MICs and MBCs tested by Scheffé post-hoc showed that the inhibitory and bactericidal activities were greatest for cefotaxime followed by cefotaxime/desacetylcefotaxime and ceftriaxone.

Because the time-kill kinetic method is considered to be more sensitive than simple MIC-MBC methodology for evaluating antimicrobial activity, it is possible to observe wide differences in the killing kinetics among strains with similar MICs (8).

Since there was no difference in the extent of killing at 6 or 24 h, the extrapolated results from the convenience plot of 6 h time-kill tested at MBC levels of drugs were considered to be predictors of the bactericidal activity. All six strains tested resisted killing by ceftriaxone in broth with 95% serum albumin. A marked negative effect of serum albumin on the killing by ceftriaxone was also demonstrated for four of six strains at a reduced, 48% equivalent serum albumin level in the testing broth. The killing rate was also slowed for two of six strains exposed to cefotaxime in broth with serum albumin.

The present study demonstrated a significant reduction in antimicrobial activity of ceftriaxone in the presence of human serum albumin (P=0.0001). In vivo animal model studies such as that of Tawara et al (27) have shown that the therapeutic efficacy of cephem antibiotics including ceftriaxone in *K pneumoniae*-induced experimental pneumonia correlated with total drug level in serum. However, in a rat model of *K pneumoniae* pneumonia described by Bakker-Woudenberg et al (28) protein binding of these antimicrobial agents in serum adversely affected both drug penetration into lungs and therapeutic efficacy.

The clinical significance of the negative effect of ceftriaxone binding to serum albumin remains controversial. While the pharmacokinetic and therapeutic efficacy data from the four clinical studies of ceftriaxone and cefotaxime (5,29-31) are equivocal in showing a difference between the two agents, Mandell et al (31) and Smith et al (32) reported that the therapeutic efficacy of ceftriaxone (2 g every 24 h) was comparable with that of cefotaxime (2 g every 6 h) in treating serious nosocomial bacterial infections.

The results of our study suggest that there was a negative influence of serum albumin on the in vitro antimicrobial activity of ceftriaxone. The clinical importance of this has not been determined.

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