

# Single daily amikacin versus cefotaxime in the short-course treatment of spontaneous bacterial peritonitis in cirrhotics

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## Abstract

**AIM:** To compare the efficacy and safety of single daily amikacin *vs.* cefotaxime in the 5-d treatment of spontaneous bacterial peritonitis (SBP).

**METHODS:** Thirty-seven cirrhotic patients with SBP, 19 in group A and 18 in group B, were studied. Group A received 1 g of cefotaxime every 6 h, and group B received 500 mg of amikacin qd. Both antibiotics were administered up to 5 d and the responses were compared.

**RESULTS:** Infection was cured in 15 of 19 patients (78.9%) treated with cefotaxime and in 11 of 18 (61.1%) treated with amikacin. Four patients of the Cefotaxime group (21.1%) and five patients of the Amikacin group (27.8%) died. Two in each group (10.5% *vs.* 11.1%) had renal impairment during study period. One in each group (5.3% *vs.* 5.6%) may be considered to suffer from nephrotoxicity due to increased urinary  $\beta_2$ -microglobulin concentration.

**CONCLUSION:** In this study, single daily doses of amikacin in the treatment of SBP in cirrhotics were not associated with an increased incidence of renal impairment or nephrotoxicity. However, a 5-d regimen of amikacin is less effective than a 5-d regimen of cefotaxime in the SBP treatment.

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**Key words:** Spontaneous bacterial peritonitis; Amikacin; Cefotaxime

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## INTRODUCTION

Some studies have suggested that liver disease is a risk factor for aminoglycoside-induced nephrotoxicity<sup>[1-4]</sup>. However, aminoglycosides are still frequently used to treat sepsis in patients with liver disease<sup>[5]</sup>. In recent studies<sup>[6-8]</sup>, single daily parenteral aminoglycoside administrations have shown some benefits as compared with multiple daily doses. These benefits include reduced toxicity, possible enhanced efficacy, greater convenience, and reduced costs. However, results of single daily aminoglycoside treatments of bacterial infections in cirrhotics have not been evaluated.

Spontaneous bacterial peritonitis (SBP) is a common complication of cirrhotic ascites. In a recent study, 5-d cefotaxime treatment of SBP was as efficacious as a 10-d course<sup>[9]</sup>.

Because of these reasons, we have designed this prospective randomized study to compare the efficacy and nephrotoxicity of single daily amikacin dosage versus that of cefotaxime in the 5-d treatment of SBP in cirrhotics.

## MATERIALS AND METHODS

### Materials

Between July 2000 and June 2002, patients admitted to the Kaohsiung Veterans General Hospital who fulfilled all of the following criteria were enrolled into this study: (1) had liver cirrhosis; (2) had an ascitic fluid absolute neutrophil count > 500 cells/mm<sup>3</sup> with SBP as the only suspected cause. Patients were excluded from the study for any of the following reasons: (1) had a history of allergy to penicillins, cephalosporins, or aminoglycoside; (2) considered to be a terminal or critical case with life expectancy of less than one month; (3) had secondary peritonitis or tumor rupture; (4) had a serum creatinine level >2 mg/dL; (5) had an antibiotic treatment during previous 2 wk.

### Methods

Patients were randomly allocated into two different therapeutic groups. Group A received 1 g of cefotaxime every 6 h. Group B received 500 mg of amikacin qd or 8 mg/kg of body weight qd if patient's body weight was less than 60 kg. The subsequent dosages of amikacin were adjusted according to renal function so that the trough level of plasma amikacin remained  $\leq 30$   $\mu$ g/mL. Both antibiotics were administered by intravenous infusion for 30 min. The antibiotics were not changed in any case during the first 72 h unless a nonsusceptible organism was isolated in the initial cultures. Antibiotics

were administered up to 5 d to patients who responded to the treatment. For patients who did not respond to the treatment after 5 d, antibiotic treatment was changed according to antibiotic susceptibility tests when a resistant organism was isolated, or empirically when the causative bacteria was not cultured.

Blood, urine, and ascites samples were obtained for culture, routine cell counts, and chemistry screening before initiation of antibiotic treatment. Other body fluids were cultured when indicated.

Abdominal paracentesis was repeated every 72 h until the culture became sterile and the ascitic fluid neutrophil count decreased to  $<250$  cells/mm<sup>3</sup>. Clinical signs and symptoms of infection, e.g., fever, chills, abdominal pain, abdominal tenderness, ileus, and mental status change, were recorded daily. Patients infected by organisms resistant to cefotaxime or amikacin were treated with appropriate alternative antibiotics according to the culture result and susceptibility tests. Two days after completion of antibiotic therapy, abdominal paracentesis was performed for culture test and cell count. Blood culture was repeated if bacteremia had been documented previously. If signs or symptoms of infection developed after discontinuation of the antibiotic, paracentesis for cell count and culture of blood were also repeated.

Infection was considered cured when all clinical and laboratory signs of infection disappeared during therapeutic period and cultures performed 2 d after antibiotic withdrawal were negative. Antibiotic treatment was considered a failure when the symptoms and signs of infection did not improve, or worsened, or when a nonsusceptible bacteria was isolated in the initial cultures. Patients discharged alive were followed closely throughout their illness for 4 wk after completion of treatment. Recurrence within 4 wk after discontinuation of therapy was defined as recurrent SBP or bacteremia. Relapse within 4 wk after discontinuation of therapy was defined as recurrent infection of ascitic fluid or blood with the same organism (identical species) that caused the initial infection. Reinfection within 4 wk after discontinuation of therapy was defined as recurrent bacteremia or recurrence of SBP with an organism different from the original pathogen. Superinfection was defined as development of SBP or bacteremia caused by a different pathogenic bacterium from the original organism during therapy. Infection-related mortality was defined as death caused by bacterial infection of ascitic fluid or blood, with clinical or bacteriologic evidence of uncontrolled infection. Hospitalization mortality was defined as death due to any cause during the hospitalization. In evaluating antibiotic efficacy, patients who died within the first 3 d after inclusion in the study were not considered.

Serum and urine creatinine levels were measured before treatment, every 2 d during treatment, and 24 h after completion of therapy. The 24-h urine was collected every 2 d for assessment of the creatinine clearance.

For patients who were treated with amikacin, blood and ascites samples for the determination of the trough and peak levels of amikacin were obtained 30 min before

and one hour after administration of the drugs for every alternate day during treatment. The samples were stored at  $-30$  °C until assay. The amikacin levels were measured by radioimmunoassay.

According to previous investigations<sup>[4]</sup>, urinary  $\beta_2$ -microglobulin is a useful test to discriminate antibiotic-induced nephrotoxicity from functional renal failure (or hepatorenal syndrome) in cirrhotic patients. Therefore, in the current study, the urinary concentration of  $\beta_2$ -microglobulin was measured in all patients studied before therapy, 3 d after initiation of treatment, and 2 d after antibiotic withdrawal. Fresh urine samples were collected and stored at pH 6 to 7 (with the addition of 1 N sodium hydroxide) and at  $-30$  °C until assayed. The analysis was performed using a commercial radioimmunoassay. Results of  $\beta_2$ -microglobulin were not available during the study.

In this study, renal impairment was defined as a rise in serum creatinine of 0.5 mg/dL or a  $\geq 50\%$  fall in creatinine clearance during the period. In the absence of other possible causes of renal tubular damage, renal impairment was considered to be secondary to nephrotoxicity if urinary  $\beta_2$ -microglobulin concentration increased from normal values (before treatment) to more than 2 000 mg/L (during treatment). Otherwise, renal impairment was considered functional. Patient who died within the first 3 d after inclusion in the study were not considered in evaluating the incidence of nephrotoxicity.

The *t*-test with Yates' correction,  $\chi^2$  with Fisher's exact test, or the nonparametric Mann-Whitney *U* test were used for statistical analysis. Data are presented as mean  $\pm$  SD. In each instance a two-tailed test was used. A *P* value of  $< 0.05$  was considered significant.

## RESULTS

A total of fifty-seven patients met inclusion criteria. Twelve patients were excluded because of either critical case with shock on presentation (4), prior treatment with antibiotics (2), initial serum creatinine concentration  $> 2$  mg/dL (4), evidence of secondary peritonitis (1), or tumor rupture (1). Forty-five patients were eligible for the study and were randomized. Twenty-two patients were randomized to cefotaxime treatment and twenty-three patients to amikacin treatment. Two patients in amikacin group were later disqualified, because secondary peritonitis and tuberculous peritonitis were diagnosed after evaluation. Three patients in each group were not considered in the analysis of the result, because they died or fled against medical advice within 48 h after entry into the study. The remaining 37 patients, 19 in cefotaxime group and 18 in amikacin group, were the subjects of this analysis.

There was no significant difference between patients of the two groups (Table 1), in relation to sex, age, etiology of cirrhosis, severity of cirrhosis as expressed by Child-Pugh score, and renal function before treatment (expressed by serum creatinine level). In each group only one patient was Child-Pugh class B. The others were class C. Only 22 patients (59.5%) had normal serum creatinine level

**Table 1** Comparison of clinical and laboratory characteristics of the patients

Characteristics	Treatment regimen		P
	Cefotaxime	Amikacin	
Number of patients	19	18	
Male/female	17/2	11/7	NS
Age(yr) <sup>1</sup>	54 ± 17	58 ± 11	NS
Etiologies of cirrhosis (%) <sup>2</sup>			NS
Alcoholism	3 (16)	2 (11)	
Chronic hepatitis B	14 (74)	11 (61)	
Chronic hepatitis C	1 (5)	4 (22)	
Child-Pugh score <sup>1</sup>	11.4 ± 1.2	11.1 ± 1.1	NS
Serum creatinine(mg/dL) <sup>1</sup>	1.5 ± 0.5	1.4 ± 0.4	NS

<sup>1</sup>Data are presented as mean ± SD. <sup>2</sup>Data are presented as number and percentage of total. NS: not significant

(<1.5 mg/dL) before treatment.

Nine (24%) of the 37 patients grew a pathogen from their ascitic fluid, and 8 (21.6%) were bacteremic. The ascites and blood isolates were similar between the two groups (Table 2). Two pathogens in the blood (group B *Streptococcus* and *Vibrio amalonaticus*) were resistant to cefotaxime and amikacin. Although the clinical signs of infection disappeared during therapeutic period with cefotaxime, crystal penicillin and tetracycline were given according to the susceptibility tests since the sixth day. The

**Table 2** Flora of ascites and blood

	Treatment regimen		P
	Cefotaxime (%)	Amikacin (%)	
<b>Ascites</b>			
<i>Escherichia coli</i>	4 (21)	3 (17)	NS
<i>Klebsiella pneumoniae</i>	0	1 (6)	NS
<i>Citrobacter diversus</i>	0	1 (6)	NS
<b>Blood</b>			
<i>Escherichia coli</i>	2 (11)	1 (6)	NS
<i>Klebsiella pneumoniae</i>	1 (5)	2 (11)	NS
<i>Streptococcus</i> group B	1 (5)	0	NS
<i>Vibrio amalonaticus</i>	1 (5)	0	NS

Data are presented as number and percentage of total. NS: not significant.

other isolates were sensitive to cefotaxime and amikacin.

The clinical response to treatment and survival were similar between the groups (Table 3). Infection was cured in 15 of 19 patients (78.9%) treated with cefotaxime and in 11 of 18 (61.1%) treated with amikacin. However, there was no statistic significance between these two groups. Three patients in cefotaxime group had recurrent infection within 4 wk after completion of treatment. One was considered relapse due to recurrent bacteremia with the same organism that caused the initial bacteremia. The other two also suffered from bacteremia, but the previous infection episode was not bacteremic. Recurrent SBP concurrent with new episodes of bacteremia rather than relapse were considered in these two patients. Among the 8 bacteremic patients in the initial treatment, 2 in the cefotaxime group had resistant isolates. Although they became well during the initial therapeutic period

and cured without recurrence within 4 wk after changing antibiotics, treatment failure was still considered according to the study's design. The other 6 bacteremic patients were bacteriologically cured by repeated culture after 5-d of antibiotic treatment. Only one patient (16.6%) in the

**Table 3** Results of treatment

	Treatment regimen		P
	Cefotaxime (%)	Amikacin (%)	
Number of patients	19	18	
Cure <sup>2</sup>	15 (78.9)	11 (61.1)	NS
Normalized PMN count <sup>2</sup>	18 (94.7)	15 (83.3)	NS
Serum creatinine(mg/dL) <sup>1</sup>	1.3 ± 0.8	1.5 ± 1.1	NS
Afebril in 72 h <sup>2</sup>	18 (94.7)	15 (83.3)	NS
Pain-free in 72 h <sup>2</sup>	19 (100)	17 (94.4)	NS
Recurrence <sup>2</sup>	3(15.8)	0	NS
Superinfection <sup>2</sup>	0	0	NS
Infection-related mortality <sup>2</sup>	0	3 (16.7)	0.105
Hospitalization mortality <sup>2</sup>	4 (21.1)	5 (27.8)	NS
Days of hospitalization <sup>1</sup>	12 ± 8	13 ± 9	NS

<sup>1</sup>Data are presented as mean ± SD. <sup>2</sup>Data are presented as number and percentage of total. NS: not significant

cefotaxime group had relapse 10 d after completion of treatment.

There was no significant difference between these two groups in the mortality rate. During the whole hospitalization period, 4 patients of the cefotaxime group (21.1%) and 5 patients of the amikacin group (27.8%) died. Although for most patients the cause of death was multifactorial, in three cases of the amikacin group infection was considered to be the main cause of death due to no other major event or infection identified.

There was no significant difference in the incidence of renal impairment or nephrotoxicity between patients treated with cefotaxime or amikacin (Table 4). Two in each group (10.5% *vs* 11.1%) had renal impairment during study period. The urinary  $\beta_2$ -microglobulin concentration increased in both groups during treatment and decreased after antibiotics withdrawal. One in each group (5.3% *vs* 5.6%) may be considered nephrotoxicity due to increased urinary  $\beta_2$ -microglobulin concentration from normal values (before treatment) to more than 2 000 mg/L (during treatment). The patient who developed nephrotoxicity in the amikacin group died on the 6<sup>th</sup> d of the study period.

**Table 4** Evaluation of nephrotoxicity

	Treatment regimen		P
	Cefotaxime(%)	Amikacin(%)	
Number of patients	19	18	
Renal impairment (%) <sup>2</sup>	2 (10.5)	2 (11.1)	NS
Urinary $\beta_2$ -microglobulin (mg/L)			
Before treatment <sup>1</sup>	402 ± 80	1220 ± 392	NS
3 d after initiation <sup>1</sup>	779 ± 2465	612 ± 814	NS
2 d after withdrawal <sup>1</sup>	126 ± 119	173 ± 44	NS
increase > 2 000 mg/L (%) <sup>2</sup>	1 (5.3)	1 (5.6)	NS

<sup>1</sup>Data are presented as mean ± SD. <sup>2</sup>Data are presented as number and percentage of total. NS: not significant.

The mortality was considered infection-related. The patient in the cefotaxime group died on the 5<sup>th</sup> d due to hepatic and renal failure even though the infection appeared under controlled.

Wide range of peak and trough levels of amikacin in patie-

**Table 5** Amikacin concentration (mean  $\pm$  SD)

Blood peak level ( $\mu\text{g/mL}$ )	19.6 – 127.3 (40 $\pm$ 32)
Blood trough level ( $\mu\text{g/mL}$ )	1.3 – 73.7 (12 $\pm$ 22)
Ascites peak level ( $\mu\text{g/mL}$ )	4.3 – 80.1 (20 $\pm$ 25)
Ascites trough level( $\mu\text{g/mL}$ )	1.2 – 78.9 (15 $\pm$ 26)

nts treated with amikacin was noted in this study (Table 5).

## DISCUSSION

The aminoglycosides are potent antibiotics, with peak concentration-dependent bactericidal activity against Gram-negative pathogens and staphylococci. They display trough concentration-dependent nephrotoxicity and ototoxicity. Aminoglycosides exhibit enduring antibacterial activity (especially against Gram-negative bacilli) many hours after tissue concentrations become negligible. Appreciation of this postantibiotic effect leads to replacement of conventional multiple daily doses by large single daily doses. The latter regimens confer at least equivalent efficacy and less risk of nephrotoxicity<sup>[7]</sup>. Among the aminoglycosides available in our hospital, we used amikacin in this study, because it is the least susceptible to degradation by bacterial enzymes and causes less nephrotoxicity than gentamicin and tobramycin<sup>[7]</sup>. Because some studies have suggested that liver disease is a risk factor for nephrotoxicity in patients treated with aminoglycoside<sup>[1-4]</sup>, we used only about half of the recommended single daily dosage of amikacin (15 mg/kg q24 h in usual study<sup>[7]</sup>) in this study.

The optimal duration of antibiotic treatment for SBP had been investigated recently. Ten to fourteen days intravenous therapy had been recommended<sup>[10-12]</sup>. However, it had been argued that, because SBP had a low bacterial load (often only 1 organism/mm<sup>3</sup> of ascitic fluid), a shorter duration of treatment might suffice. A recent randomized controlled study comparing 5 d *vs* 10 d treatment with cefotaxime found no difference in efficacy and mortality rate<sup>[9]</sup>.

In this study the cure rate was higher in the group of patients treated with cefotaxime (78.9%) than in the group of patients treated with amikacin (61.1%), although there was no significant difference. Larger sample sizes in further studies may confirm this finding. The cure rate for SBP in patients treated with cefotaxime in this study is similar to the previous studies. In Runyon's study<sup>[9]</sup>, the cure rate for SBP treated by 5-d cefotaxime is 93.1%. On the other hand, the cure rate in patients treated with amikacin in this study is also similar to the previous studies that treated cirrhotic patients with severe infection using aminoglycosides combining with other antibiotics. In Felisart's study which compared cefotaxime *vs* ampicillin-

tobramycin in cirrhotics with severe infections (most were peritonitis), the cure rates were 85% and 56% respectively<sup>[13]</sup>. The response rate in the McCormick's study which used netilmicin plus mezlocillin in the empirical therapy of presumed sepsis in cirrhotic patients was 56%<sup>[5]</sup>. Single daily dosage of aminoglycoside in the treatment of infections in cirrhotic patients seemed as effective as combining with other antibiotics in traditional dosages but less effective than cefotaxime.

It is well known that in traditional dosages, the serum, the tissue and the body fluid levels of aminoglycosides are unpredictable, varying from one patient to another<sup>[14, 15]</sup>. We conducted this study by using a single daily dose of aminoglycoside for easy monitoring of the drug level. Just like previous reports, our study also showed that there were wide ranges of drug levels in blood and ascites between the patients regardless of whether their renal function were normal or not. Some levels might not achieve the bactericidal levels. For example, the MIC of amikacin for *E coli* was 2 mg/mL in this study. Only 13 of the 18 patients (72%) had 4-fold or higher for their peak level of ascites. On the other hand, it is well established that cefotaxime has a wide range between therapeutic and toxic dosages. Also, the ascitic fluid concentration of cefotaxime is several-fold higher than the MIC of most susceptible organisms at any time throughout the treatment<sup>[16]</sup>. This may explain the difference of efficacy of treatment between cefotaxime and amikacin.

The incidence of nephrotoxicity in this present study was 5.6% in patients treated with amikacin. This was similar with the Felisart's study in patients treated with ampicillin-tobramycin (7%)<sup>[13]</sup>, but almost six times lower than the Cabrera's study in patients treated with cephalothin-gentamicin or cephalothin-tobramycin (32%)<sup>[4]</sup>. Previous investigations have suggested that combined therapy, i.e. cephalothin, might enhance the nephrotoxicity of aminoglycosides<sup>[17, 18]</sup>. Although some study suggested that the risk for aminoglycoside nephrotoxicity was 5 times higher in a patient with liver disease than without<sup>[2]</sup>, we found that a single daily dosage of amikacin did not cause marked nephrotoxicity in cirrhotic patient in this study. The incidence was between 3% and 11% in patients treated with aminoglycosides, similar with previous reports<sup>[19, 20]</sup>.

In this study, eight patients (22%) had positive blood culture concurrent with SBP. Two of them were resistant isolates to cefotaxime and had other antibiotic treatment. Six patients were all bacteriologic cured after 5-d of treatment. This was confirmed by negative culture result repeated after treatment. However, one of the six patients (17%) who was treated with cefotaxime had bacteremic relapse 10 d after completion of treatment. In Runyon's study, 9 bacteremic patients treated with 5-d cefotaxime were documented to become sterile during the first 72 h of therapy. No relapse was mentioned. 9 Because bacteremia in cirrhosis is a severe prognostic sign, it has been considered common practice to treat it for 10 to 14 d<sup>[21]</sup>. Do patients with SBP in addition to bacteremia require longer treatments than patients without bacteremia? Is a

5-d course adequate for treating bacteremia in cirrhotic patients? These issues remain to be clarified.

In spite of the lower antibiotic efficacy of amikacin, the hospitalization mortality rate resulting from this antibiotic regimen was similar to that observed in patients treated with cefotaxime. This may be explained by the fact that both groups of cirrhotics had a similar degree of liver failure. Most mortalities were related to infective complications in patients treated with amikacin and to noninfective complications in patients treated with cefotaxime.

In summary, we found that single daily doses of amikacin in the treatment of SBP in cirrhotics were not associated with an increased incidence of renal impairment or nephrotoxicity. However, the efficacy of a 5-d regimen of amikacin is less than a 5-d regimen of cefotaxime in SBP treatment.

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