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Comparison of cefotaxime and ofloxacin in treatment of spontaneous bacterial peritonitis

Spontan bakteriyel peritonit tedavisinde sefotaksim ve ofloksasin antibiyotiklerin karşılaştırılması

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Background/aims: *Gold-standard treatment of spontaneous bacterial peritonitis currently involves 3rd generation cephalosporins. To evaluate the efficacy of ofloxacin in this infection, we compared a combined therapy with intravenous and oral ofloxacin to intravenous cefotaxime.* ***Methods:*** *Thirty cirrhotic patients with spontaneous bacterial peritonitis were assigned to receive either intravenous (1 gl 12 h) cefotaxime for 7 days (n=17) or intravenous (200 mgl 12 h) ofloxacin for 2 days followed by oral (200 mgl 12 h) ofloxacin for 5 days (n=13). All cases had community-acquired spontaneous bacterial peritonitis.* ***Results:*** *The infection resolution rate on the 7th day of therapy was 82.4% in the cefotaxime group and 92.3% in the ofloxacin group. Hospital survival rates were 82.4% and 100%, respectively.* ***Conclusions:*** *Oral ofloxacin after a short course of intravenous ofloxacin is effective in the treatment of uncomplicated spontaneous bacterial peritonitis. This regimen may allow physicians to treat these patients as outpatients as soon as their intravenous therapy is completed.*

Key words: Spontaneous bacterial peritonitis, ofloxacin

Amaç: *Günümüzde spontan bakteriyel peritonit tedavisinde altın standart intravenöz 3. kuşak sefalosporinlerdir. Bu enfeksiyonda ofloksasinin etkinliğini belirlemek amacıyla intravenöz ve oral ofloksasinden oluşan kombine tedavi şemasını intravenöz sefotaksim tedavisiyle karşılaştırdık.* ***Yöntem:*** *Spontan bakteriyel peritoniti bulunan 30 sirotik hasta 2 ayrı tedavi grubuna ayrıldı [7gün boyunca intravenöz 1 gl 12 saat sefotaksim (n-17); 2 gün süresince intravenöz 200 mgl 12 saat ofloksasin ve bunu izleyen 5 gün boyunca oral 200 mgl 12 saat ofloksasin (n=13)]. Tüm hastalarda toplumsal kökenli spontan bakteriyel peritonit söz konusuydu.* ***Bulgular:*** *Tedavinin 7. gününde enfeksiyon rezolüsyon oranı sefotaksim grubunda %82.4 iken ofloksasin grubunda %92.3 bulundu. Hastane sağkalım oranları sırasıyla %82.4 ve %100 idi.* ***Sonuç:*** *Komplike olmayan spontan bakteriyel peritonit tedavisinde kısa süreli intravenöz ofloksasinin ardından oral ofloksasin uygulanması etkili bir yöntemdir. Bu tedavi rejimi doktorların hastalarını intravenöz tedavinin tamamlanmasının ardından ayaktan tedavi ile izlemelerine olanak tanıyabilir.*

Anahtar kelimeler: Spontan bakteriyel peritonit, ofloksasin

INTRODUCTION

Spontaneous bacterial peritonitis (SBP) is the infection of ascites in the absence of intraabdominal primary foci. SBP is one of the factors responsible for increased morbidity and mortality in cirrhosis.

Ten to 30% of cirrhotic patients admitted to the hospital due to ascites have SBP (1). Seventy percent of patients have a second attack within the first year of infection (2). Since SBP is fatal if left untreated, antibiotics are started as soon as possible while awaiting the culture results. The gold-standard treatment is 3rd generation cephalosporins, especially cefotaxime, at a dose of 4-8 g/day. They are very effective and lack nephrotoxicity. Duration of treatment is 7-10 days; however, in most cases resolution is achieved earlier. Resolution is obtained in 80-90% of cases (3, 4).

Mortality from SBP is still high despite earlier diagnosis and treatment. This is especially the case for severe liver failure, renal failure or hepatic encephalopathy (5, 6).

Quinolones are currently used as alternative antibiotics to cephalosporins. Ofloxacin is effective against Gram-negative bacteria. Ofloxacin has high bioavailability and can be administered both orally and intravenously, and is also cheaper than

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cefotaxime. Navasa et al. studied oral 100 mg-800 mg/day ofloxacin in comparison with 2-8 g/day intravenous cefotaxime and found no significant difference in resolution rates (7). Terg et al. compared two different ciprofloxacin schemes (400 mg/day intravenous ciprofloxacin for 7 days vs. first 2 days 400 mg/day intravenous ciprofloxacin plus 1 g/day per oral ciprofloxacin for the following 5 days) and showed results compatible with those of the largest studies done with cefotaxime (8). We aimed to compare intravenous cefotaxime with per oral and intravenous combination of ofloxacin in terms of infection resolution, efficacy, cost-effectiveness, and mortality.

MATERIALS AND METHODS

Characteristics of the patients

Thirty cirrhotic patients admitted to the emergency room and Clinics of Gastroenterology of Izmir Atatürk Teaching and Research Hospital between April 2002 and July 2003 were enrolled in the study according to the following criteria:

(1) Diagnosis of cirrhosis based on clinical, laboratory, and ultrasonography data; (2) Diagnosis of SBP based on a polymorphonuclear (PMN) leukocyte count of >250/mm^3 at admission (community-acquired SBP); (3) Absence of clinical, laboratory, and radiological data compatible with secodary peritonitis; (4) Benign cytology of ascitic fluid; (5) No current usage of corticosteroids; (6) No history of antibiotic usage within the preceding seven days despite SBP prophylaxis; (7) Serum creatinine <2 mg/dl; (8) Abscence of gastrointestinal bleeding and grade II-IV hepatic encephalopathy.

Seventeen patients were assigned to receive 1 g/12 h cefotaxime for seven days and 13 were assigned to receive 200 mg/12 h ofloxacin per oral for the first two days and intravenously for the following five days. The patients were allowed to take oral diuretics, beta-blockers, H2 blockers, and proton pump inhibitors.

Laboratory and bacteriologic studies

After SBP was diagnosed, ascitic and blood samples were taken for culture in blood culture bottles at the patient's bedside. Cultures were repeated if PMN leukocyte count was >250/mm^3 or if cultures were positive after 48 hours or seven days after starting antibiotic therapy. Antibiotic treatment was modified according to the in vitro susceptibility of the isolated microorganisms in case of treatment failure.

Blood samples were also taken for complete blood count, urea, creatinine, sodium, potassium, aspartate aminotransferase (AST), alanine aminotransferase (ALT), direct and indirect bilirubin, albumin, and total protein measurement, and ascitic fluid for albumin, total protein, lactate dehydrogenase (LDH), and glucose measurement. The same parameters were reevaluated at 48 hours and at seven days after starting antibiotic administration. Prothrombin time (PT) and international normalization ratio (INR) were also studied.

Definitions

Infection resolution was defined as ascites PMN leukocyte count <250/mm^3 and culture negativization. Treatment failure was defined as a <50% decrease in PMN leukocyte count after 48 hours of therapy, PMN leukocyte count >250/mm^3 on the 7th day of treatment, persistence of positive culture after 48 hours of therapy, and superinfection.

Statistical analysis

Comparisons between groups were performed using nonparametric Mann Whitney-U test for quantitative data and the chi square test with Fisher's exact test for qualitative variables.

Univariate analysis and multivariate analysis for variables with statistical significance ($p<0.05$) were performed to identify predictive factors for mortality. All analyses were performed with SPSS statistical software. Results are expressed as mean±SD.

RESULTS

Data of the patients

Clinical, demographic, and laboratory data of the therapeutic groups at the time of diagnosis are defined in Table 1.

Additional systemic illnesses were congestive heart failure (1 from cefotaxime vs. 1 from ofloxacin group), coronary heart disease (1 from cefotaxime group), and diabetes mellitus (3 from cefotaxime group).

Organisms were isolated from ascitic fluid and/or blood cultures in 2 (15.4%) patients from the ofloxacin group and in 6 (35.3%) patients from the cefotaxime group (Table 2) ($p=0.22$). All but one *(Acinetobacter spp.* from the cefotaxime group) of the causative microorganisms were in vitro susceptible to the assigned antibiotic. In vitro susceptibility for cefotaxime could not be studied in one patient from the cefotaxime group. Treatment was switc-

Table 1. Demographic, clinical, and laboratory data of cirrhotic patients at the time of SBP diagnosis

	CEFOTAXIME (n=17)	OFLOXACIN (n=13)	p
Gender (male)	12(67%)	6(33%)	0.17
Age (years)	51±17	48±14	0.63
Duration of cirrhosis (months)	36±48	19±18	0.23
Alcohol and/or hepatitis B	12 (71%)	9 (69%)	0.13
Child Pugh class B/C	7/10 (41/59%)	8/5 (62/38%)	0.26
Child Pugh score	11.9±2.1	10.8±2.4	0.14
Abdominal pain	10(56%)	8(44%)	0.88
Abdominal distension	12 (71%)	12 (92%)	0.14
Nausea/vomiting	10 (59%)	6 (46%)	0.49
Axillary temperature	37.3±1.0	36.8±0.7	0.13
Renal failure[a]	0	0	
Hepatic encephalopathy	3 (18%)	0	0.11
History of			
gastrointestinal bleeding	5 (29%)	4 (57%)	0.89
SBP	4 (24%)	1 (8%)	0.24
hepatic encephalopathy	4 (24%)	3 (56%)	0.97
WBC (/mm^3)	10593±5736	7519±3445	0.09
PMN leukocytes (ascites)	3135±5311	846±1995	0.16
Serum albumin (g/dl)	2.2±0.5	2.8±0.8	0.02
Ascitic fluid albumin (g/dl)	0.6±0.7	1.1±1.0	0.25
Serum bilirubin (mg/dl)	5.1±4.5	2.9±3.6	0.65
INR	2.2±1.4	1.6±0.7	0.17
Sodium (mEq/L)	132±9	135±4	0.22
Potassium (mEq/L)	4.2±0.7	3.9±0.5	0.40
Urea (mg/dl)	56±49	39±15	0.24
Creatinine (mg/dl)	1.1+0.6	0.9±0.3	0.35

a Renal failure denotes serum creatinine over 2 mg/dl.
SBP: Spontaneous bacterial peritonitis; PMN: polymorphonuclear; INR: international normalization ratio

Table 2. Bacteriologic data of ascitic fluid and blood of cirrhotic patients with SBP

	¡UEFOTAXIME (n=17)	OFLOXACIN (n=13)
Positive hemoculture	**2 (11.8%)**	**1 (7.7%)**
Gram positive	2	
Staphylococcus aureus	1	
Streptococcus viridans	1	
Pneumococcus		1
Positive ascites culture	5 (29.4%)	1 (7.7%)
Gram negative	3	1
Escherichia coli	1	1
Acinetobacter spp.	1	
Klebsiella	1	
Gram positive	2	
Staphylococcus aureus	1	
Pneumococcus	1	

hed to amoxicillin-sulbactam (SAM) according to the susceptibility test. *Stapylococcus aureus* and Escherichia coli were the predominant organisms isolated. There was no significant difference between culture positivity and response to antibiotics.

Therapeutic response

Forty-eight hours after starting antibiotics, treatment failure due to less than 50% decrease in ascitic fluid PMN leukocyte count was evident in 9 of 17 (52.9%) patients from the cefotaxime group and in 2 of 13 (15.4%) patients from the ofloxacin group (p=0.036). Of these patients, 3 (17.6%) from the cefotaxime group and 1 (7.7%) from the ofloxacin group did not achieve resolution by the 7th day of therapy (p=0.42) (Table 3). Infection resolution at the end of the treatment was 88.2% (n=12) for the

Table 3. Response to antibiotics on the 7th day of therapy

	CEFOTAXIME (n=17)	OFLOXACIN (n=13)
Resolution: culture (-) and PMN leukocyte<250/mm^3	14 (82.4%)	12 (92.3%)
Treatment failure: PMN leukocyte>250/mm^3	3 (17.6%)[a]	1(7.7%)[b]

[a]One patient had endocarditis as superinfection. *Streptococcus* viridans, which was susceptible to amoxicillin-sulbactam (SAM) in vitro, was isolated from admission hemoculture. Cefotaxime was switched to SAM. One patient had hepatorenal syndrome and probable hepatocellular cancer. Since AFP was extremely high, hepatocellular carcinoma was suspected. Ascites cytology was benign. Contrast enhanced computerized abdominal tomography and gadolinium enhanced magnetic resonance imaging yielded no tumor. None of the cultures gave positive results. The 3rd patient had no apparent cause for failure and cultures were negative. Spontaneous bacterial peritonitis (SBP) resolved with the assigned antibiotic. [b]no apparent cause for failure and cultures were negative. SBP resolved with the assigned antibiotic

cefotaxime group and 100% (n=20) for the ofloxacin group. The reasons for failure to achieve resolution are shown in (Table 3).

Antibiotic therapy was changed in only 2 (12%) patients who were assigned to receive cefotaxime. One patient received SAM and one received cefepime. After the change resolution was achieved in one patient; nevertheless, both patients died.

Course and outcome

The duration of antibiotic therapy was 8±3 and 8±2 days for the cefotaxime and ofloxacin groups, respectively (p=nonsignificant).

Three patients (17.6%) from the cefotaxime group died during hospitalization (p=0.11). The clinical complications that developed during cefotaxime and ofloxacin therapy were as follows: development or worsening of hepatic encephalopathy (2 and 0 patients, respectively), gastrointestinal hemorrhage (1 and 0 patients, respectively), superinfections (1 patient with endocarditis and 0 patients, respectively), and hepatorenal syndrome (2 and 0 patients, respectively) (p=nonsignificant). Allthe

patients from the ofloxacin group survived. The main causes of death were endocarditis, hepatorenal syndrome, and hepatocellular cancer. All clinical and laboratory data were analyzed in association with survival rate. Variables with statistical significance ($p<0.05$) in univariate analysis were introduced in a multivariate analysis. In the multivariate analysis, only sodium, AST, ALT, gammaglutamyl transferase (GGT), LDH, ALP, resolution rate on the 7th day of antibiotic therapy and hemoculture positivity were found to be statistically significant as prognostic factors (Table 4).

DISCUSSION

Ofloxacin is a very effective antibiotic against Gram-negative bacteria, the most common cause of SBP. Both oral and intravenous forms are available. We compared ofloxacin and cefotaxime in uncomplicated SBP.

In a study done by Navasa et al., oral ofloxacin (100 mg-800 mg/day) was found as effective as intravenous cefotaxime (2-8 g/day) in outpatient treatment of uncomplicated SBP (7). Terg et al. compared two different ciprofloxacin treatment schedules (400 mg/day intravenous ciprofloxacin for 7 days vs. 400 mg/day intravenous ciprofloxacin for the first 2 days followed by 1 g/day oral ciprofloxacin for 5 days) in terms of resolution and hospital survival. They found results similar to the largest studies done with cefotaxime (8).

Our ofloxacin treatment schedule was different from that of Navasa et al.: 400 mg/day intravenous ofloxacin for the first two days followed by 400 mg/day oral ofloxacin for five days. This scheme provided close observation of the patient in the hospital environment during intravenous administration. All the patients were followed in the hospital until SBP had resolved. The patients who were started on ofloxacin achieved resolution on the 7th day of treatment. Resolution rates and hospital survival rates of the cefotaxime and ofloxacin groups were similar on the 7th day of treatment (82% and 100%, respectively). Navasa et al. reported lower rates of resolution (85% for cefotaxime and 84% for ofloxacin) and hospital survival (81% for both antibiotics)7. We think that a more effective regimen with intravenous ofloxacin for the first two days was the cause of this difference. The patients who were given intravenous ciprofloxacin for the first two days of therapy had a resolution rate of 78.3% and mortality rate of 27.5% in the study done by Terg et al. (8).

We used 3 g/day of cefotaxime in our study, with a resolution rate of 82%. Cefotaxime was shown to be effective in lower doses in comparison to other studies (3, 4).

Table 4. Survival rate in cirrhotic patients with SBP

	Deaths (n=3)	Survivors (n=27)	P value
Hemoculture positivity	1 (33.3%)	23 (85.2%)	0.033
Resolution rate on the 7th day of therapy	33.3%	92.6%	0.039
AST at 48th hour of therapy	299 (76-598)	67 (16-297)	0.019
AST on the 7th day of therapy	304 (71-644)	78 (15-446)	0.034
ALT at 48th hour of therapy	77 (26-147)	36 (8-169)	0.034
GGT	90(72-125)	40(11-128)	0.020
LDH	741 (486-1078)	418 (203-860)	0.023
ALP	436(159-969)	136(69-216)	0.038
Sodium on the 7th day of therapy	127 (129-133)	134 (121-141)	0.033

In the study of Terg et al., cefotaxime was three times more expensive than intravenous ciprofloxacin and seven times more expensive than combined therapy with oral and intravenous ciprofloxacin. The cost of oral ofloxacin was 13 times lower than with intravenous cefotaxime in the study of Navasa et al. (7, 8). This cost benefit was also noted in our study, where the cost of intravenous cefotaxime was 2.4 times higher than the combined therapy of ofloxacin.

We conclude that ofloxacin in the schedule described above is a good choice in uncomplicated SBP. We think that intravenous administration for the first two days of therapy reinforces the success rate. We suggest that those patients can be discharged from hospital after two days of intravenous therapy.

The cost is also lower due to the shorter duration of hospitalization, and the oral route is a convenient means of therapy.

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