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Cefotaxime Is More Effective Than Is Ampicillin-Tobramycin in Cirrhotics with Severe Infections

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We compared the effectiveness and incidence of nephrotoxicity of ampicillin-tobramycin and cefotaxime in 73 cirrhotics who had severe bacterial infection. Most of these patients had spontaneous peritonitis and/or bacteremia. Patients were randomly allocated into two groups. Group I included 36 patients treated with ampicillin-tobramycin and Group II comprised 37 patients treated with cefotaxime. Patients from both groups were similar with respect to clinical data, standard liver and renal function tests, types of infection and isolated organisms. Ninety-two per cent of bacteria isolated in Group I and 98% of those isolated in Group II were susceptible *in vitro* to ampicillin-tobramycin and to cefotaxime, respectively. Ampicillin-tobramycin cured the infection in 56% of Group I patients, and cefotaxime in 85% of Group II patients ($p < 0.02$). Five patients treated with ampicillin-tobramycin, and none treated with cefotaxime developed superinfections ($p = 0.024$). Nephrotoxicity (impairment of renal function associated with an increase of urinary β_2-microglobulin to over 2,000 μg per liter) occurred in two patients in Group I and none in Group II. These results suggest that broad-spectrum cephalosporins should be considered as first choice antibiotics in cirrhotic patients with severe infections.

Patients with advanced cirrhosis are prone to develop severe infections, particularly spontaneous bacteremia and peritonitis. Numerous studies report the incidence, pathogenesis, diagnosis and prognosis of acute bacterial infections in cirrhosis (1–7); however, there is little information about the efficacy and complications of antibiotic treatment in these patients. In a recent investigation, in 35 cirrhotics with serious infections, the combination of cephalothin plus an aminoglycoside was effective in 58% (8). However, this antibiotic regime was nephrotoxic in almost a third of the patients.

We report the results of a randomized controlled comparison of the efficacy and incidence of nephrotoxicity of ampicillin-tobramycin and cefotaxime in cirrhotics with severe infections. The combination of ampicillin-tobramycin was selected because it has an antibacterial spectrum similar to that of cephalothin plus an aminoglycoside, but lower nephrotoxic effect (9–11). Cefotaxime, a new broad-spectrum cephalosporin, was chosen because its spectrum includes most of the organisms responsible for serious infections in cirrhotics (12–14) and is not a nephrotoxic in man at the therapeutic dosage (12, 15–17).

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PATIENTS AND METHODS

PATIENT POPULATION

The study was made in 73 consecutive cirrhotic patients with severe bacterial infection. Criteria for exclusion were a history of allergy to penicillin, cephalosporins or aminoglycosides and prior acute hypotension or therapy with antibiotics or potentially nephrotoxic drugs within a week of entry into the study.

Blood, urine and ascitic fluid cultures were routinely obtained before initiation of antibiotic treatment; other body fluids were cultured when indicated. Diagnosis of bacteremia, bacterial peritonitis or urinary tract infection was made when a positive culture of blood, ascitic fluid or urine, respectively, was obtained. The diagnosis of other infections was established by clinical, laboratory and radiological features regardless of whether the causative bacteria was isolated or not. Patients were considered to have "proved infections" if these were demonstrated bacteriologically or by clinical, laboratory or radiological data. Patients with fever and/or leukocytosis with a shift to the left but with negative cultures and without any other demonstrative evidence of infection were considered as having "possible infections." Cultures were repeated every 5 days (control cultures) and also 2 days after antibiotic withdrawal. Leukocyte count in ascitic fluid was also determined every 5 days in patients

with peritonitis. Sequential measurements of complete white blood cell count, standard liver function tests, blood urea nitrogen and serum and urine electrolytes were performed in each patient throughout the study. Serum and urine creatinine concentrations were measured daily.

ANTIBIOTIC TREATMENT

Patients were randomly allocated (random number table) into two groups: Group I included 36 patients who received ampicillin-tobramycin, and Group II included 37 patients who were given cefotaxime. The initial dosage of tobramycin was 1.75 mg per kg of body weight intravenously; subsequent doses were given intravenously every 8 hr and adjusted daily to glomerular filtration rate (GFR) according to Chan's nomogram (18). Ampicillin was administered intravenously at a dose of 2 gm every 4 hr in patients with a GFR higher than 80 ml per min. In patients with lower GFR, ampicillin dosage was adjusted daily according to creatinine clearance (2 gm every 6 or 8 hr when GFR was between 80 and 60 or between 60 and 40 ml per min, respectively, and 1 gm every 6 or 8 hr when GFR was between 40 and 20 or lower than 20 ml per min, respectively). Cefotaxime was administered intravenously following a schedule identical to that used for ampicillin.

The antibiotic therapy was not changed in any case during the first 4 days of treatment unless a nonsusceptible organism was isolated in the initial cultures. In patients who responded to treatment, antibiotics were administered up to 2 days after the disappearance of all symptoms and signs of infection. In cases who did not respond, antibiotic treatment was changed according to antibiotic susceptibility tests when a nonsusceptible organism was isolated, or empirically when the causative bacteria was not cultured.

EVALUATION OF ANTIBIOTIC EFFICACY

Infection was considered cured when all clinical and laboratory signs of infection disappeared and cultures performed 2 days after antibiotic withdrawal were negative. Failure of antibiotic treatment was considered when the symptoms and signs of infection did not improve or worsened or when a nonsusceptible bacteria was isolated in the initial cultures. Superinfection was diagnosed when a new nonsusceptible pathogenic organism was isolated in control cultures. In evaluating antibiotic efficacy, patients who died within the first 24 hr after the inclusion in the study were not considered.

EVALUATION OF NEPHROTOXICITY

Because cirrhotics are prone to develop functional renal failure (or hepatorenal syndrome), the classical criteria to diagnose antibiotic nephrotoxicity (increase of serum creatinine during the treatment) cannot be used in these patients. Previous investigations have shown that urinary β_2-microglobulin is a useful test to discriminate antibiotic-induced nephrotoxicity from functional renal failure in cirrhotic and noncirrhotic patients (8, 19, 20). Therefore, in the current investigation, the urinary concentration of β_2-microglobulin was measured in all patients studied before starting the antibiotic treatment, and afterwards in each case that developed an impairment of renal function (50% increase in serum creatinine to a level >1.3 mg per dl).

Renal impairment was considered to be secondary to nephrotoxicity if urinary β_2-microglobulin concentration increased from normal values (before treatment) to more than 2,000 μg per liter (during treatment), in the absence of other possible causes of renal tubular damage (8). Otherwise, renal impairment was considered functional. Patients who died within the first 3 days after inclusion in the study were not considered in evaluating the incidence of nephrotoxicity.

To measure the urinary concentration of β_2-microglobulin, a fresh urine sample was collected from each patient before antibiotic treatment. During therapy, urine samples were collected only in cases that developed a decrease in renal function. In these cases, urine samples were collected daily from the detection of renal impairment up to 3 days following antibiotic withdrawal. The urine was 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 (Phadebas, β_2-microtest, Pharmacia Diagnostics AB, Uppsala, Sweden). Results of β_2-microglobulin were not available during the study. Serum and urine creatinine were measured with a Technicon Autoanalyzer (Technicon Instrument Corp., Tarrytown, NY). Normal values for serum creatinine are <1.2 mg per dl.

STATISTICAL ANALYSIS

The statistical analysis of the results was performed by a Compucorp 445 Statistician digital computer (Compucorp, Los Angeles, Calif.), using the Student's t test, the nonparametric test of Mann-Whitney, and the χ^2 test. Results are expressed as mean ± standard deviation.

RESULTS

CHARACTERISTICS OF THE PATIENTS

Most of the 73 patients studied had advanced cirrhosis. At inclusion into the trial, ascites was present in 62 patients, jaundice in 47, hepatic encephalopathy in 27, active gastrointestinal hemorrhage in 18 and functional renal failure in 26. Only two patients did not show any of these abnormalities.

Tables 1 and 2 show that there were no significant differences between patients of Groups I and II in relation to age, sex, etiology of cirrhosis, clinical and laboratory data at inclusion into the trial and types of infection. There were also no significant differences between Groups I and II with respect to the number and types of isolated organisms (Table 3).

Thirty-six of the 39 bacteria isolated in Group I (92%) were susceptible *in vitro* to the combination of ampicillin-tobramycin [34 (87%) were susceptible to tobramycin and 18 (46%) were susceptible to ampicillin]. Forty-four of the 45 bacteria isolated in Group II (98%) were susceptible *in vitro* to cefotaxime.

TABLE 1. CLINICAL AND LABORATORY DATA AT INCLUSION IN THE STUDY IN PATIENTS OF GROUP I (TREATED WITH AMPICILLIN-TOBRAMYCIN) AND GROUP II (TREATED WITH CEFOTAXIME)

	Group I	Group II
No. of patients[a]	36	37
Age (yr)	54 ± 10	56 ± 11
Sex M/F (no.)	25/11	23/14
Alcoholic cirrhosis (no.)	22	18
Ascites (no.)	28	34
Hepatic encephalopathy (no.)	12	15
GI bleeding (no.)	9	9
Serum bilirubin (mg/dl)	6.3 ± 4.6	7.4 ± 10.3
Prothrombin (%)	52 ± 23	49 ± 19
Serum albumin (gm/dl)	2.5 ± 0.6	2.6 ± 0.4
BUN (mg/dl)	30 ± 27	29 ± 20
Serum creatinine (mg/dl)	1.3 ± 0.6	1.4 ± 0.8
Urinary sodium (mEq/liter)	23 ± 29	17 ± 28
Functional renal failure (no.)	11	15
Leukocyte count (per ml)	10,868 ± 6,525	10,999 ± 7,236
Neutrophil granulocytes (per ml)	9,341 ± 5,567	9,275 ± 7,207

[a] Six patients of Group I and 5 of Group II bled from esophageal varices; 3 patients of Group I and 4 of Group II bled from erosive gastritis.

TABLE 2. TYPES OF INFECTION IN GROUP I (TREATED WITH AMPICILLIN-TOBRAMYCIN) AND GROUP II (TREATED WITH CEFOTAXIME)

	Group I	Group II
Patients with proved infections[a]	29	30
No. of proved infections	41	45
Spontaneous peritonitis	20	24
Bacteremia[b]	13	13
Pneumonia	5	2
Urinary tract infection[c]	1	4
Pleural empyema	2	1
Lymphangitis	0	1
Patients with possible infections[d]	7	7

[a] Twelve patients of Group I and 13 of Group II had two simultaneous infections; one patient of Group II had three simultaneous infections.

[b] Bacteremia was secondary to peritonitis in 7 cases of each group, to pneumonia in 1 case of each group, to pleural empyema in 1 case of Group I and to urinary tract infection in 1 case of Group II. In 3 patients of Group I and 2 of Group II, bacteremia was associated with other infections (4 peritonitis, 1 urinary tract infection and 1 pleural empyema) caused by organisms different than those isolated in blood. One patient of Group I and 2 of Group II had bacteremia alone.

[c] The five cases with urinary tract infection also had other infections (3 peritonitis and 2 bacteremia).

[d] Two patients of Group I and 3 of Group II had clinical and laboratory data of peritonitis.

ANTIBIOTIC EFFICACY

Four patients from each group were not considered in analysis of antibiotic efficacy because they died within the first 24 hr of entry into the study. Of these patients, three cases from Group I and two from Group II had proved infections (2 spontaneous peritonitis and 3 bacteremia in Group I and 2 spontaneous peritonitis and 1 bacteremia in Group II). The causes of death were gastrointestinal hemorrhage in four patients, septic shock in three and hepatic failure in one. Therefore, 32 patients from Group I (26 with proved infections) and 33 from Group II (28 with proved infections) were included in the evaluation of antibiotic efficacy.

Cefotaxime was significantly more effective than was ampicillin-tobramycin (Table 4). Infection (proved or possible) was cured in 28 of 33 patients (85%) treated with cefotaxime and in 18 of 32 (56%) treated with ampicillin-tobramycin ($p < 0.02$). When only cases with proved infections are considered, cefotaxime was effective in 24 of 28 patients (86%) and ampicillin-tobramycin in 14 of 26 patients (54%) ($p < 0.02$). The proportion of proved infections cured was also significantly higher ($p < 0.01$) in patients treated with cefotaxime (33 of 42; 79%) than in those treated with ampicillin-tobramycin (17 of 36; 47%) (Table 4). The total amount of tobramycin, ampicillin and cefotaxime administered to patients of Groups I and II was 1,786 ± 784 mg, 84.1 ± 36.1 gm and 73.4 ± 31.0 gm, respectively, and the mean daily

TABLE 3. ISOLATED CAUSATIVE BACTERIA IN GROUP I (TREATED WITH AMPICILLIN-TOBRAMYCIN) AND GROUP II (TREATED WITH CEFOTAXIME)

	Group I	Group II
Escherichia coli	17	23
Klebsiella	3	5
Serratia	1	0
Proteus	1	2
Nonidentified Gram-negative bacillus	1	0
Staphylococcus aureus	3	2
Staphylococcus epidermidis	3	1
Streptococcus pyogenes	5	6
Streptococcus faecalis	1	1
Pneumococcus	4	5
Total	39	45

TABLE 4. ANTIBIOTIC EFFICACY IN PATIENTS TREATED WITH AMPICILLIN-TOBRAMYCIN (GROUP I) AND IN THOSE TREATED WITH CEFOTAXIME (GROUP II)[a]

	Group I	Group II	
Patients in whom infection was cured[b]	18 (32)	28 (33)	$p < 0.02$
Patients with proved infections in whom infection was cured[b]	14 (26)	24 (28)	$p < 0.01$
No. of proved infections cured	17 (36)	33 (42)	$p < 0.01$
Peritonitis	11 (18)	19 (22)	
Bacteremia	3 (10)	9 (12)	
Pneumonia	2 (5)	2 (2)	
Urinary tract infection	0 (1)	2 (4)	
Pleural empyema	1 (2)	0 (1)	
Lymphangitis	0 (0)	1 (1)	
Patients with possible infections in whom signs of infection disappeared	4 (6)	4 (5)	

[a] The total number of patients or infections treated are represented in parentheses.

[b] Patients with more than one infection were considered cured only when all infections were cured.

dose 216 ± 39 mg per day, 10.2 ± 2.8 gm per day and 9.2 ± 2.9 gm per day, respectively. The ratio of administered dose to theoretical dose according to renal function was calculated daily for each antibiotic in every patient. This ratio was of 1.11 ± 0.28 for tobramycin, 1.34 ± 0.47 for ampicillin and 1.10 ± 0.30 for cefotaxime, indicating that the lower efficacy of the combination of ampicillin-tobramycin could not be due to an underdosage of these antibiotics. In fact, there were no significant differences between patients of Group I who did and did not respond to antibiotics with respect to the ratios administered dose to theoretical dose of tobramycin (1.08 ± 0.29 vs. 1.15 ± 0.27) and ampicillin (1.27 ± 0.37 vs. 1.43 ± 0.24). A similar finding was observed in patients of Group II who did and did not respond to cefotaxime (administered dose to theoretical dose ratios 1.17 ± 0.37 vs. 1.09 ± 0.29).

In 10 of the 14 patients not responding to ampicillin-tobramycin, the isolated organisms were susceptible *in vitro* to at least one of these antibiotics. In two patients, the isolated organisms were resistant to both tobramycin and ampicillin, and in the other two patients, no organism was isolated. In 3 of the 14 patients not responding to ampicillin-tobramycin the antibiotic treatment was not changed because they died between the second and the fourth day after entry into the trial. In the remaining 11 patients, ampicillin-tobramycin was substituted by cefotaxime in nine patients and amikacin and cephalothin in one case, respectively. The infection was cured in seven patients treated with cefotaxime and in the case treated with amikacin. In 4 of the 5 patients not responding to cefotaxime, the isolated organisms were susceptible *in vitro* to this antibiotic. In the remaining patient no organism was isolated. In two of these patients, the antibiotic regime was not changed because they died within the second and third day, respectively, after entry into the trial. In the remaining three cases, cefotaxime was substituted by tobramycin, penicillin and the combination of ampicillin-tobramycin respectively. The infection was cured in two patients (cases treated with penicillin and tobramycin).

Five patients of Group I (16%) developed a superinfection, whereas this occurred in no patients of Group II ($p = 0.024$). In these five patients, the signs of the initial infection were not improving when superinfection was detected.

NEPHROTOXICITY

Six patients of each group were not considered in the analysis of the incidence of nephrotoxicity because they died within the first 72 hr of entry into the trial. Therefore, the incidence of nephrotoxicity was evaluated in 30 patients of Group I and in 31 of Group II. The incidence of nephrotoxicity in the current study was very low. Only two patients in Group I (7%) and none in Group II developed nephrotoxicity. One of the patients who developed nephrotoxicity died with liver and renal failure. Necropsy was not allowed. The other case developed a severe renal impairment (serum creatinine increased from a initial value of 3.1 to 9.5 mg per dl) which reverted after a few weeks. The ratios of administered dose to theoretical dose of tobramycin in these two patients were 1.08 and 0.82, respectively. Five patients in Group I (17%) and six in Group II (19%) developed functional renal impairment during antibiotic treatment.

No other side effects related to the antibiotic administration were observed in either group of patients. In addition, the mean variation between pre- and posttreatment prothrombin values in patients receiving cefotaxime (0 ± 19%) was similar to that observed in patients receiving ampicillin-tobramycin (−2 ± 16%).

MORTALITY

There was no significant difference between Groups I and II in the mortality rate. During the study period (from inclusion into the trial up to 48 hr after antibiotic withdrawal), 11 of the 36 patients in Group I (31%) and 7 of the 37 in Group II (19%) died. Although in most patients the cause of death was multifactorial, in five cases from each group infection was considered to be the main cause of death. During the whole hospitalization period, 14 patients of Group I (39%) and 10 of Group II (27%) died.

DISCUSSION

The most impressive finding of the current study was that the percentage of cirrhotics in whom the infection was cured and the percentage of infections cured were significantly higher in the group of patients treated with cefotaxime (85 and 79%, respectively) than in the group of patients treated with ampicillin-tobramycin (56 and 47%, respectively). These results suggest that cefotaxime is more effective than the combination of ampicillin-tobramycin in the treatment of severe infections in patients with cirrhosis. The observation that cefotaxime was effective in most of the patients who failed to respond to ampicillin-tobramycin further supports this contention.

The mechanism by which cefotaxime was more effective than the combination of ampicillin-tobramycin in our cirrhotics is difficult to ascertain from the present study. It was clearly not related to differences in the degree of liver impairment or in the characteristics of infections presented by patients treated with both antibiotic regimes since the two groups of patients did not differ significantly with respect to clinical and laboratory data, types of infection and isolated organisms. The observation that both antibiotic regimes showed a similar *in vitro* antibacterial activity (92% of organisms isolated in Group I and 98% of those isolated in Group II were susceptible *in vitro* to the combination of ampicillin-tobramycin and to cefotaxime, respectively) indicated that the different therapeutic response could not be attributed either to differences in the antibiotic susceptibility of the causative organisms.

There are marked differences between the pharmacology of broad-spectrum cephalosporins and that of aminoglycosides that may partially explain the different therapeutic efficacy observed with both antibiotic regimes. Cefotaxime has a wide range between the therapeutic and toxic dosages, and very high doses of this antibiotic can be given to patients with serious infections

without any adverse effect (12). In fact, it is well established that, with the therapeutic schedule used in the current study, the serum, tissue and ascitic fluid concentrations of cefotaxime are several-fold higher than the minimal inhibitory concentration of most susceptible organisms at any time throughout the treatment (21–24). On the contrary, aminoglycosides have a narrow range between the effective dosage and that which may produce nephrotoxicity and ototoxicity in a substantial proportion of patients (25, 26). When an intermittent dosage of aminoglycosides is used, as it was in the current study, it has been reported that the levels of these antibiotics at the sites of infection may be under the minimal inhibitory concentration of many susceptible organisms during the last hours of the period included between two consecutive bolus (27, 28). On the other hand, it is well known that in spite of a careful dosage, the serum, tissue and body fluid levels of aminoglycosides are unpredictable, varying widely from one patient to another (29–31). Therefore, it could be possible that, despite an adequate dosage, the levels of tobramycin were under the therapeutic concentration during relatively long periods of time in a substantial number of our cirrhotics. This feature, which might not affect the therapeutic efficacy of aminoglycosides in patients with preserved defensive mechanisms against infection, could play a critical role in the reduced response observed in the current study in patients with cirrhosis, which are known to present a defective leukocyte chemotaxis (32), low levels of serum complement (33), impaired cell-mediated immunity (34) and reduced reticuloendothelial phagocytic activity (3).

The suggestion that aminoglycosides are less effective than the broad-spectrum cephalosporins in patients with impaired defensive mechanisms against infection is also supported by other investigations. In a previous study in cirrhotic patients with severe infections, the combination of cephalothin plus an aminoglycoside was effective in only 58% of the patients (8), a figure similar to that found in the current study with ampicillin-tobramycin. On the other hand, Altucci et al. (35) have shown that the effectiveness of tobramycin in patients with leukemia of lymphoma was much lower than that observed in nonimmunodepressed patients despite a similar severity of infections in both groups of patients. Finally, of the five published randomized controlled studies comparing the efficacy of cefotaxime, or other broad-spectrum cephalosporins (cefamandole or cefoxitin) vs. aminoglycosides (administered either alone or in combination with clindamycin or carbenicillin), cephalosporins were found to be more effective than were aminoglycosides in the only study performed in patients with impaired defensive mechanisms against infection (patients with leukemia, lymphoma or solid tumors) (36), whereas no significant differences between both antibiotic regimes were observed in the remaining four studies, which included mainly cases without serious underlying diseases (37–40).

In the current study, less than 50% of the organisms isolated in patients of Group I were susceptible *in vitro* to ampicillin. This low percentage of organisms susceptible to ampicillin was, undoubtedly, another important factor in the poor therapeutic response observed in patients treated with the combination of ampicillin-tobramycin. This finding suggests that ampicillin should not be considered as a first choice antibiotic in the treatment of cirrhotic patients with severe infections.

The incidence of nephrotoxicity in our patients treated with ampicillin-tobramycin (7%) was almost five times lower than that found by Cabrera et al. in cirrhotics with serious infections treated with cephalothin plus an aminoglycoside (32%) (8). This different rate of nephrotoxicity cannot be attributed to differences in the characteristics of the patients since both series of patients were comparable with respect to clinical and laboratory data. The ratio administered dose of aminoglycoside to theoretical dose according to Chan's nomogram in the patients of Cabrera et al. and in our cirrhotics was 0.79 ± 0.29 and 1.11 ± 0.28, respectively, indicating that the lower incidence of nephrotoxicity in the current study was not due to the administration of a lower dosage of tobramycin. In the present investigation, there were more patients with spontaneous bacterial peritonitis than in the study of Cabrera et al. However, it is unlikely that this difference may justify the distinct rate of nephrotoxicity occurring in both series of patients. The most likely explanation for the high frequency of nephrotoxicity in the study of Cabrera et al. is that all their patients were given cephalothin, which has been shown to enhance the nephrotoxicity of aminoglycosides (9–11). As could be anticipated from previous investigations (12, 15–17), no patient treated with cefotaxime in the current study developed nephrotoxicity.

In contrast to the distinct rate of nephrotoxicity found in the current study as compared to that found by Cabrera et al., the incidence of functional renal impairment did not differ greatly in these two series of patients. Functional renal impairment (decrease in renal function without a significant rise in urinary β_2-microglobulin) occurred in 17% of our cirrhotics and in 25% of patients studied by Cabrera et al.

In spite of the lower antibiotic efficacy of ampicillin-tobramycin, the mortality rate of cirrhotics treated with this antibiotic regime was similar to that observed in patients treated with cefotaxime. These apparently paradoxical results could be explained by the fact that antibiotic treatment was properly changed in most patients not responding to ampicillin-tobramycin. On the other hand, both groups of cirrhotics had a similar degree of liver failure. Therefore, it is not surprising that the mortality rate related to infective and noninfective complications was similar in the two groups of patients.

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