Türk Nefroloji Diyaliz ve Transplantasyon Dergisi/Office Journal of the Turkish Nephrology, Association 1999;4:195-199

IMIPENEM/CILASTATIN TREATMENT IN CAPD PERITONITIS

SAPD PERİTONİTİNİN TEDAVİSİNDE IMIPENEM/CILASTATIN

Arif Kapuagasi*, Canan Ağalar*, Murat Duranay, Mehmet Tuğrul Sezer***, Ahmet Elaldı*, Ruchan Türkyılmaz***

Depts of Clinical Microbiology and Infectious Diseases* and Internal Medicine** Social Security Hospital, ANKARA
Süleyman Demirel University, School of Medicine, Dept of Internal Medicine*** İSPARTA

ÖZET

Amaç: *Bu çalışmada, sürekli ayaktan periton dializi (SAPD) uygulanan 50 son dönem böbrek yetmezliği olan hastanın bir yıldaki 88 peritonit atağında imipenem/cilastatin tedavisinin etkinliği araştırıldı.*

Metod: *Mikrobiyolojik inceleme için bifazik Castenada besiyeri (kan kültürü sistemi), kanlı agar ve Mc Conkey agar (plak metodu) kullanıldı. Tüm hastalara imipenem/cilastatin ampirik olarak başlandı. Tedavi, ilk gün Ig intravenöz yükleme dozu ve takip eden dokuz gün iki litre diyaliz solüsyonuna 100 mg imipenem/cilastatin olacak şekilde uygulandı. Diyaliz solüsyonundaki PMNL sayısının mm3'de 100'ün altında olması primer yanıt olarak kabul edildi.*

Sonuçlar: *imipenem/cilastatin tedavisinde, sırası ile primer yanıt, nüks ve tamamen tedavi oranları %93, %4, %89 olarak bulundu. Mikroorganizma izolasyonu yönünden kan kültürü sistemi (%77) plak metoduna (%43) göre daha duyarlı bulundu. Staphylococcus epidermidis (50%), E. Coli (17%), Staphylococcus aureus (13%) and Klebsiella spp. (7%) en sık izole edilen mikroorganizmalardı.*

Sonuç: *İmipenem/cilastatin, SAPD peritonitinin ampirik tedavisinde oldukça etkilidir.*

Anahtar kelimeler: Imipenem/cilastatin, SAPD, peritonit, klinik çalışma.

ABSTRACT

Objectives: *In this open trial, the efficacy of imipenem/cilastatin was investigated in 88 peritonitis episodes in 50 chronic renal failure patients on continues ambulatory peritoneal dialysis (CAPD) in one year.*

Methods: *Biphasic Castenada medium (Blood culture system), blood base agar and Me Conkey media (plate method) were used for microbiological determination. Imipenem/cilastatin was used as the empirical therapy in all patients. One g loading dose of Imipenem/cilastatin IV was given to all patients at the first day. 100 mg Imipenem/cilastatin in 2 liter dialysis solution was administered to all patients as the standard therapy for the following 9 days. Primary response was accepted to occur when PMNL number in the dialysis solution decreased to 100/mm3.*

Results: *Primary response, relapse and overall cure rate were 93%, 4%, 89% respectively in imipenem/cilastatin treatment. Blood culture system (77%) was found to be more sensitive than plate method (43%) in isolating the micro-organisms which were as follows in order of decreasing frequency: Staphylococcus **epidermidis** (50%), E. Coli (17%), Staphylococcus aureus (13%) and Klebsiella spp. (7%).*

Conclusion: *It can be concluded that Imipenem/cilastatin first-line treatment is highly efficient in CAPD peritonitis.*

Key words: Imipenem/cilastatin, CAPD, peritonitis, clinical trial.

This paper was presented in the 9th European Congress of Clinical Microbiology and Infectious Diseases, Berlin.

INTRODUCTION

Continuos ambulatory peritoneal dialysis (CAPD) is used in the treatment of uraemic patients since mid 1940 (1). Peritoneal inflammation is the most frequent complication of CAPD (2). Mono or combined antibiotic therapy are used for treatment of CAPD via parenterally, intraperitoneally or orally. Today, vancomycin, amikacin and cephalosporins are widely used in CAPD peritonitis (3). Vancomycin-amikacin combination therapy is accepted as gold standard (4-6). Serious side effects such as ototoxicity and neuromuscular paralysis are the major disadvantages of this therapy.

Imipenem/cilastatin is highly effective against the pathogens isolated from peritoneal dialysis solution of patients with CAPD peritonitis (7-9). It is demonstrated in pharmacokinetic studies that high blood and peritoneal dialysis solution levels were achieved (7,10). Patient compliance to monotherapy may be more better than combined therapy. Moreover, imipenem/cilastatin has advantages on most of the combination therapies in regards to ototoxicity and nephrotoxicity.

Therefore, the purpose of this study was to evaluate the efficacy of imipenem/cilastatin in patients with CAPD peritonitis.

PATIENTS AND METHOD

Eighty-eight peritonitis episodes in 50 patients with CAPD were evaluated in one year period. Variables such as gender, antibiotic usage, the period between the time of beginning of CAPD and first episode of peritonits, the isolated pathogens, and the efficacy of imipenem/cilastatin in these episodes were evaluated.

One g of imipenem/cilastatin was administered to all patients in 100 ml of saline with IV infusion as an initial loading dose. In consecutive 10 days 100 mg imipenem/cilastatin was added to 2L of dialysis solution. Informed consent to participate in the study was obtained from patients themselves.

Ten ml of dialyzate was inoculated in blood culture medium (Biphasic brain-heart infusion media, Oxoid). Another 10 ml sample was centrifuged in 2000 rpm for 5 minutes period. After this period the sediment was inoculated to 5% Blood Agar Base and Eosin Methylene Blue Agar (EMB) mediums. Giemsa stained fresh samples were also prepared. Plate cultures were incubated at 37 "C for 24-48 hours. Blood culture mediums were incubated at 37 "C for *7*> days with daily observations. Isolates were identified by using standard procedures. Antibiotic resistance testing were done by using Kirby Bauer disk diffusion method.

To test the clinical and bacteriologic response 3rd, 5th and 10th days of therapy WBC counts from dialysis solution samples were re-evaluated.

Patients with peritonitis having systemic symptoms and micro-organisms such as *S.aureus, Candida* spp and *Pseudomonas* spp were hospitalized. Otherwise they were treated on ambulatory basis. At 5th day patients whose symptoms were not improved and WBC were not decreased were accepted as treatment failure. Alternative therapies were carried out according to antibiotic susceptibility test results. The subsiding of peritoneal inflammation findings within 10 days and the decrease in the number of PMNL's under 100/mm3 was defined as primary response. The recurrence of the findings of peritoneal inflammation within 14 days after the completion of antibiotic therapy was defined as relapse. Cure was accepted if the peritonitis subsided and any relapses were seen after 14 days of the completion of therapy.

Chi-square test was used for statistical analysis.

RESULTS

In this study 88 CAPD peritonitis episodes in 30 male and 20 female patient were evaluated. Fifty-two episodes were occurred in male while 36 occurred in female. The clinical findings of CAPD peritonitis were given in **Table I.**

Table I. The clinical findings of patients.

	Number (n=)	**%**
Turbid dialysis solution	**88**	**100**
Abdominal pain	**80**	**91**
Nausea- vomiting	**18**	**20**
Fever (>37.5^{0}C)	**5**	**6**
Hypotension- shock	**2**	**3**

The first peritonitis episode occurred within the first twelve month after CAPD was carried out in 86% of cases. Sixty-eight (77%) micro-organisms were isolated from 88 peritonitis episodes **(Table II).** All of these micro-organisms grew in blood culture system. Only 43% (n:38) of cultures performed with plate method grew micro-organisms. It is shown that blood culture system is more sensitive than plate method in regards to finding of positive culture (p=0.007). After centrifuging the dialysis solution, under alight microscope with Giemsa staining, micro-organisms were detected in 7 % (n:6) of episodes. Cultures grew gram positive and negative bacteria in 66% and 31%,

respectively. Coagulase negative Staphyloccoci was the most common bacteria isolated (50%). *E. Coli, S. Aureus, Klebsiella* spp were detected in 16%, 13%, 7%, respectively **(Table III).** *Candida* spp were isolated in two patients. One of them was diabetic and the other had an history of antibiotic use for long time. All of the bacteria were found to be sensitive to imipenem/cilastatin in vitro.

Table II. Comparison of blood culture system and plate method.

Culture methods	**Culture positive**		**Culture negative**	
	n	**%**	**n**	%
Blood culture system	**68***	**77**	20	23
Plate culture method	**38***	**43**	50	57

*p=0.007

Table III. Micro-organisms isolated from peritoneal fluid samples

Micro-organism	**number**	**%**
Gram positive bacteria	**45**	**66**
Coagulase negative staphylococcus	**34**	**50**
Coagulase positive staphylococcus	**9**	**13**
Enterococcus	**2**	**3**
Gram negative bacteria	**21**	**31**
E.coli	**11**	**16**
Klebsiella	**5**	**7**
Enterobacter	**2**	**3**
Acinetobacter	**2**	**3**
Pseudomonas spp	**1**	**1**
Candida spp	**2**	**3**

To assess the efficacy of therapy, dialysis solution samples were cultured at day 3rd, 5th, and 10th day after the initiation of antibiotic therapy. At the third day cultures were negative in 49 of 68 patients (72%). After treatment with imipenem/cilastatin primary and complete cure rate were 93%, 89% **(Table IV).** Any adverse effects were encountered. Four patients who responded to therapy after 3rd day of imipenem/cilastatin treatment experienced relapse. In these patients 2 methicillin resistant *S Aureus* (MRSA), one methicillin resistant coagulase negative staphylococcus (MRSE), one *Klebsiella* spp were isolated. These patients responded to alternative antibiotic therapy. In patient with MRSE relapse, exit site infection was also encountered (Table V). Among those patients who did not respond to treatment three had *S. Aureus* (2 MRSA, 1 MRSE), and 2 had *Candida* spp isolated. Two patients having *Candida* spp and one patient with MRSA did not respond to alternative therapies, so their catheters were withdrawn. In the patient who had MRSA and did not respond to therapy exit site infection was also encountered **(Table VI).**

Table **IV.** The response of peritonitis episodes to imipenem/cilastatin.

	Number (n=)	**%**
Primary response	**82**	**93**
Failure	**6**	**7**
Relapse	**4**	**4**
Total cure	**78**	**89**

Table V. Relapses after imipenem/cilastatin treatment.

Number	**Micro-organism**	**Outer site infection**	**Result**
2	MRSA	-	Responded to ancomycin.
1	MRSE	+	Responded to ancomycin.
1	Klebsiella	-	Responded to amikacin + imipenem/cilastatin.

Table VI. The course of peritonitis that did not response to imipenem/cilastatin

Number	**Microorganism**	**Outer site infection**	**Result**
1	MRSA		Responded to vancomycin and amikacin
1	MSSA	_	Responded to vancomycin.
1	MRSA	+	Didn't respond to vancomycin and amikacin. Catheter withdrawal was done.
1	MRSE		Responded to vancomycin.
2	Candida spp	_	Didn't respond to Amr'otericin B. Catheter withdrawal was done.

DISCUSSION

Peritonitis is the most important complication of CAPD. Before 1980 the number of the episodes of CAPD peritonitis was high, but in recent years the increase in experience and knowledge cause significant decreases in the number of peritonitis episodes (1-3 episodes/year) (11,12). CAPD peritonitis generally occurs with in the first year of dialysis (11). The type of micro-organism in CAPD peritonitis resemble to each other in different dialysis units and different geographical patterns. 55-80% of isolates are gram positive micro-organism. Coagulase negative staphylococcus is the most encountered (30-45%) pathogen. Gram negative bacteria are also frequently encountered. These are responsible in 20-30% of CAPD peritonitis. Candida peritonitis is not frequent and it is more encountered in patients using long term antibiotic therapy (3,11,12). In the present study 66% of pathogens were gram positive and 31% were gram negative bacteria. The most encountered pathogen was the coagulase negative Staphylococcus. One patient with peritonitis caused by *Candida* spp was diabetic and the other had an history of long term antibiotic use. This finding confirms with the literature finding.

Vancomycin, cephalosporins and aminoglycosides are frequently used in CAPD peritonitis. Clinical success rate is 84-90% with these drugs (4,5,20,21). Lupo et al found in their comparative trial that teicoplanin and tobramycin combination was superior to cephalotin and tobramycin combination (22). But ototoxicity emerged as an important shortcoming of this combination (11,20,23). With vancomycin and ceftazidime combination therapy clinical success rate reached up to 92% with fewer adverse effects (20). Gucek et al compared cefazolin and netilmycin versus vancomycin and ceftazidime in the treatment of CAPD peritonitis and demonstrated any significant difference (24).

It is known that most of the cephalosporins have deleterious effects on growth of the peritoneal mesothelial cells. It is difficult to assess the pathogens in peritoneal dialysis solution with standard culture procedures. The dilution of the pathogen in the dialysis solution, phagocytosis of the pathogen by polymorphonuclear leukocytes and macrophages, entrapment of bacteria by fibrin clotting, and history of previous antibiotic use are important mechanisms in this regard (4,12-17). Culture negative peritonitis rate differs from 3% to 42% among centerres regarding to the microbiologic culture methods that are used (4,11,12,18). Long term antibiotic use and pathogens such as *Mycobacterium tuberculosis* that is requiring specific culture methods also effects the rate of culture negative peritonitis (4,12). The rate of culture negative peritonitis decreased by using the methods such as inoculation of the dialyzate sediment after centrifuging the sample, direct inoculation of the sample to the blood culture media or large volume sample inoculation technique (11,12,16,19). It is possible to identify the pathogens in 43-85% of peritonitis (20). Jean et al compared the blood culture system and plate method in CAPD peritonitis and found that blood culture system was more sensitive than plate method (90% vs 63%) (19). The present study has reached to similar results. In 77% of episodes pathogens were being able to identified by blood culture method whereas this figure decreased to 43% in plate method. Peritoneal mesothelial cells plays important roles in tissue repair and regeneration mechanisms. Vancomycine, tobramycine and imipenem/cilastatin have any adverse effects in this regard (25). Merchant et al demonstrated that imipenem/cilastatin monotherapy is effective as vancomycine and amikacin combination therapy (26). Lui et al used imipenem/cilastatin one g IV as a loading dose and thereafter 20 mg per 2 L peritoneal dialysis solution in 30 peritonitis episodes and found primary response rate 90% and total cure rate 73%. In the same study they found the rate of 95% for primary cure and 85% for total cure when they applied one g of imipenem/cilastatin as a IV loading dose and there after 100 mg of imipenem/cilastatin per 2 L of peritoneal dialysis solution (7). We reached the similar results to that of done by Lui et al (7).

In conclusion, in suspicion of peritonitis in a CAPD patient direct microscopy with gram staining and after sampling for culture, imipenem/cilastatin empirical therapy is a preferable choice.

REFERENCES

1. Levison ME, Bush LM. Peritonitis and other intra-abdominal infections. In Principles and practice of infectious diseases. Ed. Mandel GL, Douglas RG, Bennet JE. 3rd edition Churchill Livingstone Inc. 1990, pp 636-670.
2. Fenton S.S.A, Pei Y, Delmore T, Cattran DC, Bowman C, Johnstan N, Campbell 1, Clarke WT, Richardson RM. The CAPD peritonitis rate is not improving with time. ASAIO Trans 1986;32(l):546-9.
3. Horton MW, Deeter RG, Sherman RA. Treatment of peritonitis in patients undergoing continous ambulatory peritoneal dialysis. Clin Pharm. 1990;9(2): 102-8.
4. Karchmer AW. Approach to the patient with infection in a prosthetic device. In Gorbach SL, Bartlett JG,

Blacklow NR (eds), Infectious Diseases, International ed.,W.B. Saunders Company USA, 1992, pp 1374-84.

5. Hagelskjaer LH, Moller JK. Peritonitis in continous ambulatory peritoneal dialysis. An evaluation of the empiric initial antibiotic treatment. Ugeskr Leager, 1996;158(18):2532-7.
6. Moller JK, Hagelskjaer LH. Peritonitis in continuous ambulatory peritoneal dialysis. Culture of peritoneal dialysis solution fluid. Ugeskr Leager 1996;! 58(18):2538-41.
7. Lui SF, Cheng AB, Leung CB, Wong KC, Lai KN. Imipenem/cilastatin sodium in the treatment of continuous ambulatory peritoneal dialysis-associated peritonitis. Am J Nephrol 1994;14:182-6.
8. Sobel JD,. Imipenem and aztreonam. Infect Dis Clin North Am. 1989;3:613.
9. Wilson SE. Carbapenems: Monotherapy in intraabdominal sepsis. Scand J Infect Dis. suppl 1995;96:28.
10. Chan CY, Lai KN, Lam AW, Li PK, Chung WWM, French GL. Pharmacokinetics of parenteral imipenem/cilastatin in patients on continuous ambulatory peritoneal dialysis. Journal of Antimicrobial Chemotherapy 1991;27:225-32.
11. Saklayen MG. CAPD peritonitis, incidence, pathogens, diagnosis and management. Med Clin North Am 1990;74(4):997-1010.
12. Levision ME, Bush LM. Peritonitis and other intra-abdominal infections. In Mandell GL, Douglas RG, Bennet JE (eds), Principles and Practice of Infectious Diseases, 3rd ed., Churchill Livingstone UK, 1990, pp 636-670.
13. Hachler H, Vogt K, Binswanger U, von Graevenitz A: Centrifugation of 50 ml of peritoneal fluid is sufficient for microbiological examination in continuous ambulatory Peritoneal dialysis patients with peritonitis. Infection 1986;14:102-4.
14. Holley JL, Bernardini J, Piraino B: Continuous cycling peritoneal dialysis is associated with lower rates of catheter infections than continuous ambulatory .peritoneal dialysis. Am J Kidney Dis 1990; 16:133.
15. Males BM, Walshe JJ, Garinger L. Addi-Check filtration, BACTEC and 10 ml culture methods for recovery of micro-organisms from dialysis effluent during episodes of peritonitis. J Clin Microbiol 1986;23:350.
16. Poole-Warren LA, Taylor PC, Fannel PC. Laboratory diagnosis of peritonitis in patients treated with continuous ambulatory peritoneal dialysis. Pathology 1986;18:237-9.
17. Taylor PC, Poole-Warren LA, Grundy RE. Increased microbial yield from continuous ambulatory peritoneal dialysis effluent after chemical or physical Distruption of Phagocytes. J Clin Microbiol 1987;25:580-3.
18. Lye WC, Wong PL, Leong SO, Lee WJ. Isolation of organisms in CAPD peritonitis: a comparison of two techniques. Adv Perit Dial 1994;10:166-8.
19. Holley JL, Moss AH. A prospective evaluation of blood culture versus standard plate tecniques for diagnosis peritonitis in continuous ambulatory peritoneal dialysis. Am J Kidney Dis 1989; 13(3): 184-8.
20. Beaman M, Solaro L, McGonigle RJS, Micheal J, Adu D. Vankomycin and ceftazidime in the treatment of CAPD peritonitis. Nephron 1989;51:51-5.
21. Bistrup C, Siboni AH, Pedersen RS. Peritonitis among patients treated with continuous ambulatory peritoneal dialysis. Ugeskr Leager, 1995; 157(28):4023-6.
22. Lupo A, Rugiu C, Bernich P, Laudon A, Marcantoni C, Mosconi G, Cantaluppi MC, Maschio G. A prospective, randomised trial of two antibiotic regimens in the treatment of peritonitis in CAPD patients: teicoplanin plus tobramycin versus cephalothin plus tobramycin. J Antimicrob Chemother 1997;40(5):729-32.
23. Vas SI. Treatment of Peritonitis. Peritoneal Dialysis International, 1994;14(3):49-55.
24. Gucek A, Bren AF, Hergouth V, Lindic J. Cefazolin and netilmycin versus vancomycin and ceftazidime in the treatment of CAPD peritonitis. Adv Perit Dial 1997;13:218-20.
25. Yen CJ, Tsai TJ, Chen HS, Fang CC, Yang CC, Lee PH, Lin RH, Tsai KS, Hung KY, Yen TS. Effects of intraperitoneal antibiotics on human peritoneal mesothelial cell growth. Nephron 1996;74(4):694-700.
26. Merchant MR, Anwar N, Were A, Uttley L, Tooth JA, Gokal R. Imipenem/cilastatin versus netilmicin and vancomycin in the treatment of CAPD peritonitis. Adv Perit Dial 1992;8:234-7.