IS TIGECYCLINE EFFECTIVE IN CONTINUOUS AMBULATORY PERITONEAL DIALYSIS RELATED PERITONITIS

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ABSTRACT

Introduction*: To compare conventional intraperitoneal vancomycin-amikacin and intravenous tigecycline treatments for continuous ambulatory peritoneal dialysis (CAPD) related peritonitis.*

Materials and methods*: Patients diagnosed with CAPD-related peritonitis were randomized into two groups as intravenous tigecycline group (n=10) and intraperitoneal vancomycin-amikacin group (n=20). Patients accompanied by peritonitis exit site infection, peritonitis based on Pseudomonas or fungi were excluded from the study.*

Results*: As for 24th and 48th hours peritoneal fluid leukocyte count of patients, significant difference was not observed in tigecycline group at 24th hours, while significant reduction was observed in vancomycin-amikacin group (p<0.05). A significant reduction was observed at 48th hours in both groups. As for the treatment response, abdominal pain decreased in 18 (90%) patients in vancomycin-amikacin group, decreased in 8 (80%) patients in tigecycline group at 48th hours. It was detected that dialysate leukocyte count decreased significantly (p>0.05). Relapse was observed in 4 (40%) patients in tigecycline group, while not observed in vancomycin-amikacin group (p<0.05).*

Conclusion*: Tigecycline proved its effectiveness in the clinical use for complicated intra-abdominal infections. However, it was considered that tigecycline cannot be alternative to vancomycin-amikacin treatment for continuous ambulatory peritoneal dialysis related peritonitis.*

Keywords*: Tigecycline, vancomycin, continuous ambulatory peritoneal dialysis, peritonitis.*

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Introduction

End-stage renal disease is a clinical picture characterized by irreversible loss of endogenous renal function. Continuous dialysis or renal transplantation is necessary for protection against life-threatening uremia. Peritoneal dialysis is an important alternative for the treatment of patients with end-stage renal disease. Despite all technical developments, peritonitis continues to be the most important complication in continuous ambulatory peritoneal dialysis (CAPD). Of the patients who receive CAPD, 15-35% are admitted to hospital with peritonitis. The rate of encountering peritoneal dialysis is 45% in the first six months, whereas 60 to 70% in the first year of CAPD. The probability for recurrence of peritonitis is 20-30%[1,2]. Infection is a major cause of mortality and morbidity in patients undergoing peritoneal dialysis.

Tigecycline, which is a minocycline derivative, is an glycylcycline group antibiotic, primarily approved in the treatment of complicated skin and soft tissue infections and complicated intra-abdominal infections by the US Food and Drug Administration.

In 2009, it has been also approved for the treatment of community originating pneumonia developing from sensitive pathogens[3-5]. Although it structurally resembles tetracyclines, it is not affected by two major bacterial resistance mechanisms developed against tetracyclines. Today, in a time where the development of new antibiotics decreases, it is stated in several clinical studies that tigecycline demonstrates efficiency against many gram-positive and gram-negative bacteria and therefore constitutes an important alternative for the treatment of mild to moderate infections. During tigecycline treatment, renal dose adjustment is necessary for patients with severe hepatic insufficiency as the primary route of elimination is biliary elimination. The secondary route of elimination is renal elimination and glucuronidation[6,7].

Administration of another drug does not affect the use of tigecycline in the cytochrome P450 family of enzymes. No clinically significant drug interactions were observed during the concomitant use of digoxin and warfarin. The most frequently reported adverse effects associated with the use of tigecycline are nausea and vomiting. These untoward effects are dose limiting and are not diminished by a slowing of the rate of drug infusion[8]. Nausea as an adverse effect to tigecycline usually occurs in the first 1-2 days of treatment and is transient in most patients. Diarrhea was also reported in a significant number of patients (13%) in phase 3 clinical trials, but no tigecycline treated patient tested positive for Clostridium difficile toxin or developed C. difficile–associated diarrhea.

One case of C. difficile-associated diarrhea was reported from a phase 2 clinical trial of patients with complicated intra-abdominal infections[9]. Skin reactions with tetracyclines are not common but may be made manifest as pruritis, urticaria, and maculopapular rashes. Cross-sensitization occurs with this class of antibiotics; therefore, anyone reporting an allergy to one of these agents should be considered hypersensitive to tigecycline.

Vancomycin is preferred for the empirical treatment of CAPD-related peritonitis in many centers. However, increased use of vancomycin poses a risk for vancomycin-resistant S. aureus and vancomycin-resistant enterococcal infections. Therefore, guidelines recommend the avoidance of vancomycin therapy if possible[10].

The purpose of the present study was to compare conventional intraperitoneal vancomycin-amikacin and intravenous tigecycline treatments for CAPD-related peritonitis.Figure

Materials and methods

Study Design

This prospective, randomized, single-blind study has been conducted in accordance with the principles of the Helsinki Declaration and approved by the local Institutional Review Board (17.12.2011/4). Written informed consent was obtained from all subjects.

A total of 55 patients, admitted to the Department of Nephrology of our tertiary center with the diagnosis of peritonitis between January 2011 and February 2012 constituted the study group. Of the 55 cases, 36 patients at the age of 18 or older which were being monitored in the CAPD unit were included in the study.

Infectious peritonitis was diagnosed if at least two of the following were present:

• Signs and symptoms of peritonitis (abdominal pain, fever, chills, by just nausea, vomiting, diarrhea);

• Blurred peritoneal fluid leukocyte count of 100 cells / mm^3> and if more than 50% of the cells are polimorphonuclear leukocyte (PMN);

• Culture-positive and / or positive Gram staining[10,11].

A detailed history was obtained on arrival of the patients. Systemic questions and detailed physical examinations were performed. Each peritonitis attack was treated as a separate case. Patients accompanied by infections of the peritonitis exit, fungal and Pseudomonas-induced peritonitis (due to the known weak activity of tigecycline on Pseudomonas) were excluded from the study. Six patients did not fulfill the inclusion criteria and excluded from the study. As a result, 30 patients were included in the study.

Each patient was randomized into a group in such a manner that each one had the same empirical chance of being administered one of the two drugs. Tigecycline group (n=10) was treated with 1x100 mg dose of tigecycline followed by a 2x50 mg daily intravenous administration; vancomycin-amikacin group (n=20) was treated with 15-30 mg/kg van-

comycin every 5 days+2 mg/kg amikacin daily.

Outcome Parameters

The day the patients diagnosed with peritonitis was accepted as day 0. White blood cell, hemoglobin, hematocrit, platelets, erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), alanine aminotransferase, aspartate aminotransferase, urea, creatinine, total protein, albumin blood levels were recorded. The physical examination of the patients, cell counts and typing (with Giemsa) was performed daily. Cultures were re-collected from patients who have not shown a sufficient clinical and laboratory response to treatment on the 48th hour and the 5th day.

The results of the treatment, the complications and deaths were recorded. The primary endpoint was the decline of the peritoneal fluid blur after 48 hours of treatment and reduction in the number of cells as well as the regression in the findings of the infection. The complete disappearance of the signs and symptoms of peritonitis was considered as 'cured' or 'recovered', whereas the persistence of these signs and symptoms after the treatments was regarded as a failed treatment. The secondary endpoint was, reappearing peritonitis attacks within 4 weeks after the completion of the treatment which was considered as relapse, reappearing attacks within 4 weeks with different microorganisms were considered as recurrence whereas patients who did not respond to the treatment within 5 days were considered refractory peritonitis.

The treatment was continued with tigecycline as long as no tigecycline resistant strain was discovered in the antibiogram. In the vancomycin+amikacin group, amikacin was removed in case a Gram positive and sensitive strain proliferation was observed in the culture result and the treatment was continued with vancomycin. In case of a Gram negative proliferation, other modifications were performed in relation to the condition of sensitivity under consideration of the recommendations made by the International Society for Peritoneal Dialysis 2010 Guide. Blurring control of the peritoneal fluid and the cell count was assessed daily.

Statistical Analysis

Data were analyzed using the IBM Statistical Package for Social Sciences v15 (SPSS Inc., Chicago, IL, USA). Parametric tests (Chi-square and Fisher's exact chi-square tests) were applied to data of normal distribution and non-parametric tests (T-test, Mann-Whitney and Wilcoxon tests) were applied to data of questionably normal distribution. Continuous data were presented as mean±standard deviation. All differences associated with a chance probability of 0.05 or less were considered statistically significant.

Results

A total of 55 patients have been followed in the peritoneal dialysis program at the Department of Nephrology in our hospital during the study. A total of 36 patients developed peritonitis attack in the monitoring period. Six patients did not fulfill the inclusion criteria and excluded from the study. One of these cases had active P. aureginosa proliferation, whereas the other five cases have infections at the exit of the disease and where therefore not included in the study. As a result, 30 patients (14 males and 16 females) with a mean age of 53.36±11.18 years were included in the study.

Tigecycline group included 10 patients (4 males, 6 females) with a mean age of 55.2±8.75 years. Vancomycin-amikacin group included 20 patients (10 males, 10 females) with a mean age of 52.45±12.32 years. Both groups did not differ from each other by means of age ($p>0.05$) and gender ($p>0.05$). The demographic characteristics of the patients are given in Table 1.

	Total (n:30)
Age	53.36±1.18
Gender (male/female)	14/16
Peritoneal dialysis duration (year)	3.53±0.55
Number of peritonitis attack	2.06±1.25
Body mass index	26.08±0.81

Table 1: The demographic properties of patients being monitored with a peritonitis diagnosis.

The mean WBC level of the study group was 10511.66±738.41/mm^3 (range 3700/mm^3 to 22640/mm^3). Of the 30 patients, 20 had a WBC level lower than 11000/mm^3, five had a WBC level between 11000 and 15000/mm^3, and five had a WBC level higher than 15000/mm^3. The WBC level was 11586±4599/mm3 in the tigecycline group, and 9974±3746/mm^3 for vancomycin-amikacin group.

The mean hemoglobin level was 10.4±0.369 g/dL for the whole study group, 10.87±2.15 g/dL for tigecycline group, and 10.20±1.97 g/dL for vancomycin-amikacin group. The mean blood platelets level was 348366±21410/mm^3 for the whole study group, 362500±105003/mm^3 for tigecycline group, and 341300±124939/mm^3 for vancomycin-amikacin group.

No statistically significant differences were observed between the two groups regarding complete blood count parameters (p>0.05). The mean ESR level was 88.5±4.134 mm/h for the whole study group, 87.70±22.39 mm/h for tigecycline group, and 88.90±22.39 mm/h for vancomycin-amikacin group. The mean CRP level was 73.91±60.99 mg/L for tigecycline group, and 68.07±44.60 mg/L for vancomycin-amikacin group. No statistically significant differences were observed between the two groups regarding CRP values (p>0.05). The categorical evaluation of the C-reactive proteins was observed within normal limits in one patient, between 5-50 mg/L in 15 patients, 50-100 mg/L in eight patients and above 100 mg/L in six patients. The patients with CRP levels over 100 mg/L had severe clinical findings on admission.

The mean peritoneum fluid leucocyte count was 3511.33±760.17/mm^3 for the whole study group, 4662±5213/mm^3 for tigecycline group, and 2912±3558/mm^3 for vancomycin-amikacin group (Figure 1).

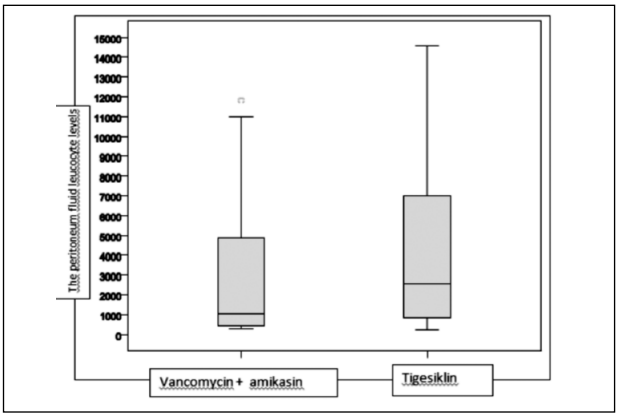

Fig. 1: The peritoneum fluid leucocyte levels of the cases.

The difference was not statistically significant (p>0.05). The determined mean neutrophile level percentage via Giemsa staining was 77.10±21.31 for tigecycline group and 67.75±13.71 for vancomycin-amikacin group. Dispersion of microorganism breeding peritonitis fluid culture on vancomycin-amikacin and tigecycline groups are shown in Table 2. Breeding in culture was not detected on two patients followed in the tigecycline group.

	Total (n:28)	Tigecycline arm (n:8)	Vancomycin + amikacin arm (n:20)
Coagulase-negative staphylococcus	16 (57,1%)	6 (75%)	10 (50%)
S. aureus	4 (14,3%)	1 (12,5%)	3 (15%)
Streptococcus	4 (14,3%)	-	4 (20%)
Enterococcus	1 (3,6%)	-	1 (5%)
E. Coli	2 (7,1%)	1 (12,5%)	1 (5%)
Y. enterocolitica	1 (3,6%)	-	1 (5%)

Table 2: Microorganisms isolated from peritoneal culture.

As for the treatment response, if the first endpoint is considered, four patients (13.3%) had abdominal sensitivity during the examination performed at the 48th hour, whereas the 26 patients (86.7%) displayed regressing clinical findings. Two patients with abdominal sensitivity (20%) were in tigecycline group, the other two (10%) were in vancomycin-amikacin group (p>0.05).

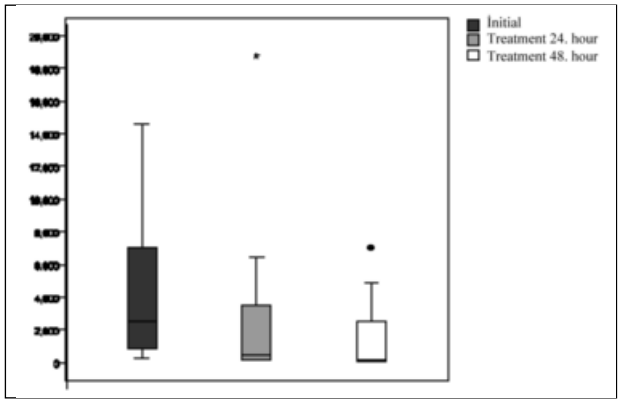

Fig. 2: The initial peritoneum fluid leucocyte levels in the 24th and 48th hours of the tigecycline group.

If the initial 24th and 48th hour peritoneum fluid leucocyte counts of the vancomycin-amikacin group are considered, no significant decrease was observed in tigecycline group on the 24th hour (p>0.05), whereas a significant decrease was observed in the vancomycin-amikacin group (p<0.05) (Figure 2, 3). A significant decrease was present in the peritoneal fluid leucocyte counts of both groups at the 48th hour (Table 3).

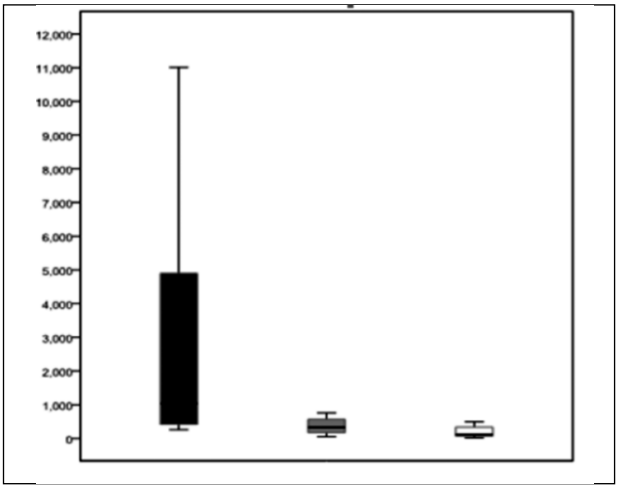

Fig. 3: The initial peritoneum fluid leucocyte levels in the 24th and 48th hours of the vancomycin-amikacin group.

	İnitial	24.hour	48.hour
Tigecycline	4662±1648.58*	3108±1860.06	1534±787.37
Vancomycin-amikacin	2912±795.63ᵋ	703±258.48	240.5±63.41

Table 3: Mean dialysate leucocyte counts (mm3) in the tigecycline and vancomycin-amikacin groups at the 24th and 48th hours.
*p<0.05 initial- 48. hour, ᵋp<0.005 initial- 24.hour ve 48. hour

The investigation of the patients regarding catheter loss revealed that three patients (10%) had a catheter loss due to refractory peritonitis and that all displayed gram negative factors. One patient (10%) in tigecycline group and two patients (10%) in vancomycin-amikacin group had a catheter loss (p>0.05).

In the evaluation regarding relapse of the patients, four out of 10 patients (40%) in tigecycline group had a relapse whereas no relapse was observed in vancomycin-amikacin group. The difference between two groups was statistically significant (p<0.05). Vancomycin-amikacin treatment was started in four cases of the tigecycline group which had a relapse. CoNS proliferated in three of the cases which had a relapse, whereas S. aureus proliferated in one case. The amikacin administration of the patients was stopped and the treatment was continued with vancomycin and the cases recovered completely.

Although there was no unresponsiveness during the treatment follow-up in the group undergoing tigecycline treatment, a high rate of relapse was observed soon after the discontinuation at treatment. By considering cathetering loss and peritoneum reserve of the patients, this group of the study was terminated after the 10th patient.

Discussion

Nowadays, CAPD is one of the modern methods used for the treatment of late stage renal failure. CAPD is increasingly preferred because it provides constant biochemical values, contributes to fluid balance, provides an active lifestyle independent from the dialysis center, not requires vascular input and anticoagulation, enables for better control of anemia, preserves residual renal function and costs less than hemodialysis. However, the peritonitis developing in these patients still continues to be the most severe complication. The frequency of peritonitis differs among countries and centers. The incidence of peritonitis determined by the Turkish Nephrology Association was 1/79.8 month for the year 2013[12].

The first vancomycin resistant Staphylococcus strain in the world has been isolated from an end-stage renal failure patient. Many centers prefer vancomycin for the empirical treatment of CAPD-related peritonitis. Increased use of vancomycin poses a risk for vancomycin-resistant staphylococcus and vancomycin-resistant enterococcal infections.

Therefore, guidelines recommend to avoid of vancomycin therapy[10]. Today, in a time where the development of new antibiotics decreases, tigecycline demonstrates efficiency against many gram-positive and gram-negative bacteria and therefore constitutes an important alternative for the treatment of mild to moderate infections. Tigecycline has been primarily approved for the treatment of complicated skin and soft tissue infections and complicated intra-abdominal infections. Tigecycline is a medication which demonstrated its efficiency in complicated intraabdominal infections as soon as it was put in clinical use and is especially interesting because it does not require renal dose adjustment and displays only low drug interaction.

In the beginning of the study, a comparison on a total of 40 patients was planned between vancomycin-amikacin treatment, which is known for its efficiency, but that has to be utilized rationally due to its resistance development, and tigecycline, which is effective against gram positives such as methicillin resistant staphylococcus, vancomycin-resistant enterococci as well as gram negatives such as extended spectrum beta lactamase positive.

When we reached 20 cases, the intermediate analysis demonstrated that the tigecycline group had higher relapse rates than the vancomycin-amikacin group. A significant decrease in the leucocyte count was observed in the vancomycin-amikacin group at the 24th hour, whereas no significant decrease was observed in the tigecycline group at the 24th hour. A significant decrease was observed in the peritoneum fluid leucocyte counts of both groups at the 48th hour. The tigecycline group was terminated after 10 cases in order to preserve the peritoneum reserve of the patients and to prevent probable catheter losses.

However, the tigecycline antibiotics susceptibility in every isolated peritonitis strain was worked and susceptible to tigecycline was observed in all isolated strains. Even though it has been reported that intraperitoneal treatment is superior to intravenous treatment, there are previous studies who demonstrate an equal efficiency for both treatments[13]. Although it is sensitive in vivo, no data related to the intraperitoneal administration of tigecycline was present during the period of study, the tigecycline was administered intravenously. This is considered to be the reason for a high relapse rate. Intraperitoneal treatment is being recommended in the ISDP 2010 Guidelines since it reaches higher local concentrations and is more effective than intravenous treatment. Again, it was considered that the presence of a biofilm on the catheter and the insufficient access of tigecycline to the peritoneum catheter may have caused these relapses.

In a study conducted by Robiyanto et al., the stability, pH, color change and precipitation of the various peritoneum dialysis solutions of tigecycline were analyzed and it has been determined that the drug concentration can be sustained in the 216th, 72nd and 8th hours at a 90% higher level than the initial values and that no precipitation or significant pH and color changes were present. The results obtained by this study constitute a platform for future studies aiming to determine the safety and treatment efficiency of intraperitoneal tigecycline in the treatment of CAPD-related peritoniti[14].

C-reactive protein as well is an inflammation indicator, its serum level increases during many conditions such as bacterial infections and inflammations. It is considered that high CRP levels in peritoneum dialysis patients is an effective indicator for the determination of cardiovascular disease and mortality risks[15-17]. In addition, high CRP levels have been observed to increase distinctively during the development of peritonitis as well[18]. The CRP levels are generally a parameter reflecting the severity of the inflammation as well.

However, the meaning of the elevation during peritonitis has not been understood yet. In a study conducted by Hind et al., elevated CRP was observed in all patients who were monitored due to peritonitis, but no significant relationship was established between the risk factors. In addition to this, it has been pointed out that the highest values were observed during two peritonitis episodes which developed due to E. coli and Candida strains. Resistant microorganisms and recurrent peritonitis episodes have been observed in patients with ongoing CRP elevation. It has been considered that, the CRP levels are important during the monitoring of treatment response, that high values may indicate a catheter-related infection and may be associated to peritonitis related mortality[18]. In the present study, all patients except one were observed to have elevated CRP.

The peritonitis developed in CAPD-related peritonitis patients still continues to be the most severe complication. The prevention of peritonitis development and decreasing its frequency will provide CAPD patients with a longer life of higher quality. Another important point is the successful treatment of developed peritonitis episodes. Increased use of vancomycin poses a risk for vancomycin-resistant Staphylococcus and vancomycin-resistant enterococcal infections.

Conclusion

Tigecycline is a medication which demonstrated its efficiency in complicated intraabdominal infections as soon as it was put in clinical use and is especially interesting because it does not require renal dose adjustment and displays only low drug interaction. However, our study has concluded that especially the intravenous administration of tigecycline constitutes no alternative for vancomycin-amikacin treatment for the treatment of CAPD-related peritonitis. New studies are needed regarding the intraperitoneal administration of tigecycline.

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