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Original Article

Oral teicoplanin for successful treatment of severe refractory *Clostridium difficile* infection

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Abstract

Introduction: *Clostridium difficile* is the leading cause of hospital-acquired diarrhoea. There is no defined protocol for treating severe *Clostridium difficile* infection (CDI) refractory to vancomycin or vancomycin and metronidazole combination therapy. The aim of this study was to evaluate the rate of clinical cure, time to resolution of diarrhoea and recurrence rate in patients with severe refractory CDI treated with oral teicoplanin.

Methodology: A one-year prospective study was carried out in the Clinic for Infectious and Tropical Diseases, Clinical Center Serbia. Patients with severe and complicated CDI who failed to respond to oral vancomycin and intravenous metronidazole combination therapy were enrolled. They were given oral teicoplanin 100 mg bi-daily. Patients were followed for recurrence for eight weeks.

Results: Nine patients with a mean age of 70.8±9.4 years were analyzed. All patients had pseudomembranous colitis, and five had complicated disease. In four patients intracolonic delivery of vancomycin was also performed in addition to oral vancomycin and intravenous metronidazole prior to initiating teicoplanin, but without improvement. After teicoplanin initiation all patients achieved clinical cure. The mean time to resolution of diarrhoea after teicoplanin introduction was 6.3±4.5 days. There was no statistically significant difference in time to resolution of diarrhoea according to initial leucocyte count, age over 65 years, the presence of ileus, complicated disease and the use of concomitant antibiotic therapy (p = 0.652, 0,652, 0.374, 0.374, and 0,548, respectively). None of the patients experienced recurrence.

Conclusions: Oral teicoplanin might be a potential treatment for severe and complicated refractory CDI, but further studies are required.

Key words: oral teicoplanin; *Clostridium difficile*; refractory pseudomembranous colitis; recurrence.

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Introduction

Clostridium difficile infection (CDI) is the most common cause of hospital-acquired diarrhoea [1]. Oral vancomycin is the first choice treatment for severe CDI, while combination of intravenous metronidazole and oral vancomycin is the suggested treatment for severe complicated disease [1]. With the emergence of the new, hypervirulent strain NAP1/BI/027 more severe illness is reported, as well as more cases of refractory to standard therapy [2]. Despite existing guidelines, there is no defined protocol for treating severe refractory CDI, and literature data comes from individual case reports with different treatment approaches. Intravenous tygecyclin, intravenous immunoglobulins, oral vancomycin in higher doses, and vancomycin enema are some of the suggested treatment regimens but they were all applied to a small number of patients [3-6]. Oral teicoplanin is another antibiotic, which was proven to be successful in the treatment of patients with CDI, including those with severe disease [7,8]. Previous studies have not analysed the role of teicoplanin in the treatment of refractory disease.

In this study we report our experience with teicoplanin in the treatment of patients with severe and severe complicated CDI who failed to respond to vancomycin and vancomycin and metronidazole combination therapy. The aim of the study was to evaluate the rate of clinical cure, time to resolution of diarrhoea and recurrence rate in patients with severe refractory CDI treated with oral teicoplanin.

Methodology

The study was performed in the Clinic for Infectious and Tropical Diseases, Clinical Centre Serbia in Belgrade, from 1st August 2013 until 31st

July 2014. Patients with severe or severe complicated CDI who failed to respond to a 14-day treatment regimen with oral vancomycin and intravenous metronidazole were enrolled into the teicoplanin study. Patients with other bowel diseases (malignancy, inflammatory bowel diseases, and different kinds of enteropathy), were excluded.

The diagnosis of CDI was indicated by the presence of diarrhoea and a positive enzyme immunoassay test for detection of *C. difficile* toxin A and B in stool [RIDAQUICK *Clostridium difficile* Toxin A/B (R-Biopharm AG, Darmstadt, Germany)]. Stool specimens were collected in sterile containers and sent to the Hospital microbiology laboratory where they were stored at 4°C and processed within 24 hours. In order to confirm the diagnosis of CDI, endoscopy was performed in each patient prior to initiation of therapy. All analysed patients had an endoscopy finding of pseudomembranous colitis.

Diarrhoea was defined as three or more unformed stools per day and time-to-resolution of diarrhoea as the period of time to less than three formed stools per day after teicoplanin was initiated [9]. Clinical cure was defined as resolution of diarrhoea with no reappearance of unformed stools during treatment. Recurrence was diagnosed in patients with the reappearance of diarrhoea within eight weeks after therapy was completed.

A severe episode of CDI was diagnosed by endoscopic evidence of pseudomembranous colitis or by two or more of the following criteria: leucocyte count of above 15 000 cells/mm^3, rise of serum creatinine level (at least 1.5 times the premorbid level), hypoalbuminaemia (< 30 g/l) and fever ≥ 38.5°C. Severe and complicated CDI was diagnosed by the presence of ileus, toxic megacolon, hypotension requiring the use of vasopressors, and/or end organ failure (renal failure, respiratory failure) [1]. Ileus was diagnosed in patients with radiological signs of bowel distension followed by vomiting or stool absence, and toxic megacolon was diagnosed by radiological signs of colon distension (> 6 cm in transverse width) and signs of severe systemic inflammatory response [9].

All patients who fulfilled the inclusion criteria were initially given oral vancomycin 125mg q6h for severe CDI and oral vancomycin 500 mg q6h plus intravenous metronidazole 500mg q8h for severe complicated form of the disease. If patients with severe CDI did not improve after 7 days of vancomycin monotherapy, intravenous metronidazole was added. If this combination therapy did not result in clinical cure after 14 days of treatment, oral teicoplanin was introduced. The dose of teicoplanin was 100 mg bi-day for at least 14 days. Patients were given vials orally for parenteral use because oral formulation of neither teicoplanin nor vancomycin was available in Serbia. Vials were reconstituted with sterile water for injection in the Clinical pharmacy and stored at 2-8°C for the maximum of 24 hours.

The Ethical committee of Clinic approved the study for Infectious and Tropical Diseases. Patients (or caregivers) signed a written, informed consent. The study was performed according to the declaration of Helsinki and subsequent revisions [10].

All data were analysed using the methods of descriptive and analytic statistics. Student`s t-test was performed for parametric data. Statistical Package for the Social Sciences (SPSS) software for Windows (version 17.0) was used for statistical analysis. Statistical significance was set at 0.05.

Results

During the study period, a total of 102 patients with severe or severe complicated CDI treated with vancomycin or vancomycin plus metronidazole were hospitalized in the Clinic for Infectious and Tropical Diseases, Clinical Centre Serbia. Nine of the 102 (8.8%) patients failed dual therapy, met the inclusion criteria and were included in the analysis.

The mean age of analysed patients was 70.8±9.4 years. All patients had colonoscopic evidence of pseudomembranous colitis prior to initiation of standard therapy. In five cases endoscopy was repeated after unsuccessful combination therapy upon introduction of teicoplanin and pseudomembranes were verified again in all patients. Clinical, demographic and laboratory characteristics of patients are shown in Tables 1 and 2.

In four patients with ileus intracolonic delivery of vancomycin was performed in addition to vancomycin and metronidazole combination therapy, before teicoplanin introduction. Vancomycin 500 mg in 150 ml saline q6h was given as retention enema for 7 days, but without improvement. After introducing teicoplanin to these patients, ileus resolved in 3.8 ±1.3 days. In one of the five patients with complicated CDI, the disease worsened during combination therapy and the patient developed respiratory failure on the fourteenth day of treatment. After teicoplanin introduction, this patient improved, stools formed and respiratory failure subsequently resolved. The description of this and other patients' characteristics on admission, prior to initiating teicoplanin and during teicoplanin therapy is shown in Table 1.

Table 1. Clinical and laboratory characteristics of patients with refractory CDI treated with teicoplanin on admission, at teicoplanin introduction and during teicoplanin therapy (n=9)

	Characteristics on admission			**Characteristics at the moment of teicoplanin introduction**			**Characteristics during teicoplanin therapy**			
Pt	Signs and symptoms	Laboratory findings	Initial therapy and duration	Clinical characteristics and complications	Baseline laboratory and otherfindings	Disease severity	Concomitant infection and antibiotic therapy	Time to resolution of ileus/toxic megacolon	Time to resolution of diarrhoea	Laboratory and clinical findings after 7 days
1	Abdominal tenderness, fever, diarrhoea	Le 19600/mm^3 Alb 28 g/L CRP 275mg/mL Cr 328 µmol/L	V for 7 days V + M for 7 days	Abdominal tenderness, fever, diarrhoea, ascites, peripheral oedema	Le 16900/mm^3 CRP 210 mg/L albumin 23g/L Cr 201 µmol/L pseudomembranes	Severe	No	NA	2 days	Le 10 000/mm^3 CRP 130 mg/mL Alb 26 g/L Ascites in regression No oedema
2	Abdominal tenderness, fever, diarrhoea, ileus	Le 16 700/mm^3 Alb 25 g/L CRP 287mg/mL Cr 278 µmol/L	V+M for 14 days, V enema 7 days	Abdominal tenderness, diarrhoea, peripheral oedema, ileus, acute renal failure	Le 12800/mm^3 Alb 23 g/L CRP 243 mg/L Cr 349 µmol/L	Severe complicated	No	3 days	9 days	Le 8900/mm^3, CRP 97 mg/mL, Cr 105 µmol/L, renal failure resolved Regression of oedema
3	Abdominal tenderness, fever, diarrhoea	Le 14700/mm^3 Alb 28 g/L CRP 185mg/mL Cr 165 µmol/L	V for 7 days, V +M for 7 days	Diarrhoea	Le 10900/mm^3 Alb 33g/L, CRP 80 mg/L, Cr 86µmol/L pseudomembranes	Severe	No	NA	1 day	Le 7800/mm^3 CRP 37 mg/mL Alb 36 g/L
4	Abdominal tenderness, fever, ileus, ascites, pleural effusion	Le 18 300/mm^3 Alb 25 g/L CRP 235mg/mL Cr 96 µmol/L	V + M for 14 days V enema for 7 days	Abdominal tenderness, fever, ascites, pleural effusion, toxic megacolon, respiratory failure, hypotension requiring vasopressors	Le 23900/mm^3 Alb 18g/L CRP 527 mg/mL Cr 190 µmol/L	Severe complicated	Sepsis-Klebsiella sp; imipenem, vancomycin i.v.	4 days	8 days	Le 11 000/mm^3 CRP 186 mg/mL No need for vasopressors Ascites and pleural effusions in regression No need for ventilator support
5	Abdominal tenderness, ascites, pleural effusion	Le 12 000/mm^3 Alb 24 g/L CRP 198mg/mL Cr 101 µmol/L	V+M for 14 days	Abdominal tenderness, fever, ascites, pleural effusion, peripheral oedema, ileus	Le 15000/mm^3 CRP 367 mg/mL Cr 71 µmol/L pseudomembranes	Severe complicated	No	6 days	16 days	Le 13200/mm^3 CRP 163 mg/mL Ascites, pleural effusion in regression
6	Abdominal tenderness, fever, ascites, ileus	Le 16 700/mm^3 Alb 22 g/L CRP 321mg/mL Cr 234 µmol/L	V +M for 14 days V enema 7 days	Abdominal tenderness, fever, ascites, ileus	Le 16900/mm^3 Alb 22g/L CRP 288 mg/mL Cr 160 µmol/L	Severe complicated	No	3 days	5 days	Le 10 300/mm^3 CRP 117 mg/mL Minimal ascites
7	Abdominal tenderness, ascites, pleural effusion, ileus	Le 17 000/mm^3 Alb 24 g/L CRP 280mg/mL Cr 296 µmol/L	V +M for 14 days V enema for 7 days	Abdominal tenderness, fever, ascites, pleural effusion, toxic megacolon, hypotension requiring vasopressors	Le 27000/mm^3 Alb 21g/L CRP 348 mg/mL Cr 375 µmol/L	Severe complicated	Pneumonia; imipenem	3 days	3 days	Le 11 700/mm^3 CRP 132 mg/mL Cr 154 µmol/L No need for vasopressors Ascites in regression
8	Abdominal tenderness, diarrhoea	Le 15800/mm^3 Alb 27 g/L CRP 176mg/mL Cr 332 µmol/L	V for 7days V + M for 7 days	Abdominal tenderness, fever, diarrhoea	Le 12600/mm^3 Alb 22g/L CRP 92 mg/mL Cr 168 µmol/L pseudomembranes	Severe	Urinary tract infection - Enterococcus sp; vancomycin	NA	6 days	Le 8700/mm^3 CRP 62 mg/mL Cr 144 µmol/L
9	Abdominal tenderness, fever, diarrhoea	Le 19700/mm^3 Alb 26 g/L CRP 163mg/mL Cr 114 µmol/L	V for 7days V+M for 7 days	Abdominal tenderness, diarrhoea	Le 21200/mm^3 Alb 21g/L Cr 92 µmol/L pseudomembranes	Severe	No	NA	7 days	Le 13 700/mm^3 CRP 45 mg/mL Alb 25 g/L

Pt- patient; Le –leucocyte count; Alb- albumin; CRP- C reactive protein; Cr - creatinine; V – vancomycine; M –metronidazole; NA –non aplicable

All patients treated with teicoplanin achieved clinical cure. The mean time to resolution of diarrhoea after teicoplanin was introduced was 6.3±4.5 days. Eight patients required 14 days of teicoplanin treatment while the ninth patient's diarrhoea resolved only after 16 days of teicoplanin therapy for a total of 21 days of treatment (Table 1). The improvement of patients' condition was accompanied by the improvement in laboratory analyses (Table 1). There was no statistically significant difference in time to resolution of diarrhoea according to initial leucocyte count > 15 000 cells/mm^3 (p = 0.652) or any of the analysed variables (Table 3). No recurrence was observed during follow-up.

Discussion

Severe CDI is an important health care issue, with the rate of treatment failure reaching 14.2% in patients treated with vancomycin [11]. The elevation of minimum inhibitory concentration (MIC) of vancomycin and metronidazole for *C. difficile* might explain the failure of standard therapy [12]. Refractory CDI is an increasing problem in everyday practice, but although there are many studies addressing CDI therapy, there is little data about treatment of patients with severe disease who failed to respond to intravenous metronidazole and oral vancomycin. Prolonged hospitalization in refractory CDI leads to higher mortality risk in these patients, not only due to

Table 2. Clinical and demographic characteristics, comorbidity and laboratory analyses of patients with severe and severe complicated refractory CDI treated with teicoplanin at the moment of teicoplanin introduction (n = 9)

Clinical and demographic characteristics	Number of patients
First CDI episode	7
Age > 65 years	7
Male	5
Fever ≥38.5°C	6
Abdominal tenderness	8
Complicated disease	5
Ileus	5
Toxic megacolon	2
Hypotension requiring the use of vasopressors	2
Renal failure	1
Respiratory failure	1
Concomitant infection and the use of concomitant antibiotics	3
Comorbidity	
Cardiovascular disease	7
Diabetes	4
Previous ischemic stroke	4
Previous surgery	3
Immobility	8
Baseline laboratory analyses	Mean ± SD
Leukocyte count (cells/mm^3)	17 500 ± 10 900
Albumin (g/L)	22.6 ± 4.4
Creatinine level (μmol/L)	188.0 ± 109.3
C reactive protein (mg/L)	269.5 ± 148.4

Table 3. Time to resolution of diarrhea according to different clinical and demographic characteristics of patients with refractory severe or severe complicated CDI (n = 9)

Patients' characteristic	Number of patients	Time to resolution of diarrhea in days (mean ±SD)	*P* value[a]
Age > 65 years	7	7.1 ± 5.9	0.652
Age ≤ 65 years	2	5.0 ± 4.2	
With ileus	5	8.2 ± 7.0	0.374
Without ileus	4	4.8 ± 1.7	
Severe complicated CDI	5	8.2 ± 7.0	0.374
Severe non-complicated CDI	4	4.8 ± 1.7	
With concomitant antibiotic therapy	3	5.0 ± 3.0	0.548
Without concomitant antibiotic therapy	6	7.5 ± 6.3	

[a] Univariate analysis was performed to evaluate the difference in time to resolution of diarrhea according to different clinical and demographic characteristics

CDI itself but also due to other healthcare associated infections, thromboembolism etc. Therefore, it is extremely important to find a solution for patients with refractory CDI.

In this study we demonstrated successful treatment with teicoplanin of severe, and even severe and complicated refractory CDI. All patients were initially treated with standard therapy for 14 days, but did not reach clinical cure, or were worsening despite therapy, which was the reason to switch to another treatment option.

Teicoplanin is a glycopeptid antibiotic with high in-vitro activity against *C. difficile* [13]. The MIC of teicoplanin for *C. difficile* is fourfold lower than the MIC of vancomycin, which might explain the efficiency of teicoplanin in the treatment of patients with CDI who failed to respond to vancomycin [13].

Few studies, which analysed the use of oral teicoplanin in the treatment of CDI, showed its success [7,8]. The achieved clinical cure rates were 96% and 96.2%, while recurrence rates were 7% and 7.7% [7,8]. Clinical cure rate was higher and recurrence rate lower in patients treated with teicoplanin compared to those treated with vancomycin [7,8]. These studies included patients with moderate and severe disease, but all were conducted before the global spread of CDI and before the emergence of NAP1/BI/027 strain and did not include patients with complicated or refractory disease [7,8].

We were the first to analyse the effect of oral teicoplanin in patients refractory to standard therapy. All of them had severe disease and all achieved clinical cure. It might be discussed whether prolonged standard therapy would eventually result in clinical cure in these patients. The fact that in five patients endoscopy verified the persistence of pseudomembranes after 14 days of standard therapy undoubtedly means that the initial therapy was not adequate, and that teicoplanin therapy was the one that resulted in clinical cure. It is important to emphasize that this study also included patients with complicated CDI who are usually excluded from clinical studies and who represent one of the major treatment problems. All five patients with refractory complicated disease also achieved clinical cure after being given oral teicoplanin.

Time to resolution of diarrhoea among our patients was longer than in studies with vancomycin and fidaxomycin, but this could be explained by the fact that we analysed only patients with severe disease who were refractory to standard therapy and were, therefore, difficult to treat. [11]. In a report by Herpers *et al.* who also analysed refractory CDI, time to resolution of diarrhoea was from three to seven days after alternative regimen with tigecycline was introduced, similar as in our study [3]. Although time to resolution of diarrhoea was prolonged, in our patients with complicated disease ileus resolved faster, three to six days after teicoplanin introduction.

Another point that should be highlighted is that all teicoplanin-treated patients not only achieved clinical cure but also did not experience recurrence during follow-up. Recurrence did not occur despite risk factors of being over 65 years old and/or concomitant antibiotic therapy. High recurrence rates represent one of the most important issues in management of CDI. Risk of first recurrence is 24%-25.3% and 13.3%-15.4% in vancomycin and fidaxomycin treated patients, respectively [11]. The risk of second and subsequent recurrence can reach 40%-65% [1]. The fact that our study included both patients with first episode of CDI and those with first recurrence makes the absence of recurrence even more significant. It can be argued whether the absence of recurrence was the result of longer overall therapy or of teicoplanin usage itself. There are no studies so far which show benefits of prolonged therapy over standard 10-14 day treatment, and even more, it is considered that unnecessarily longer treatments should be avoided in order to prevent further disruption of intestinal microflora [14].

Limited data is available about successful non-surgical treatment of complicated refractory CDI. There are several reported cases of successful treatment with intravenous tigecycline, alone or in combination with vancomycin [3]. Other authors demonstrated that intravenous immunoglobulins might also contribute to the improvement of these patients if given in addition to oral vancomycin [4].

Another therapeutic option for severe refractory CDI is intracolonic delivery of vancomycin by rectal enema [6]. Kim *et al.* showed that the majority of patients who were given intracolonic vancomycin had complete resolution of symptoms although subsequently, two developed severe recurrence with fatal outcome [6]. Among our patients, four were given intracolonic vancomycin in addition to standard therapy before initiation of teicoplanin, but this did not result in clinical cure.

In latest guidelines fidaxomycin was approved for treatment of severe CDI, with clinical cure rate of 82% in these patients [9,11]. Fidaxomycin is more expensive than teicoplanin, and is not approved for

treatment of complicated disease, nor was it evaluated as potential therapy for refractory CDI [9,11].

This study has potential limitations. Observations are made on a small number of patients. We did not perform PCR ribotyping so it remained unknown whether teicoplanin would also be successful in the treatment of CDI caused by ribotype 027. Faecal concentrations of teicoplanin were not measured, but considering the favourable outcome it is assumed that they were higher than MIC for *C. difficile*.

Conclusion

According to the above-mentioned, oral teicoplanin might be a potential treatment for refractory CDI. It could be used for severe as well as for complicated disease. We demonstrated its efficacy in patients with first episode of CDI but also in patients with first recurrence, in those with concomitant antibiotic therapy and even in those who were critically ill. No recurrences or treatment failures were observed, but this should be taken with caution due to the small number of patients. Further studies, preferably randomized clinical trials are required in order to define the role of teicoplanin in the treatment of severe CDI.

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