Case Report

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Local application of fidaxomicin in a patient with subtotal colectomy following recurring *Clostridium difficile* infection

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Introduction: *Clostridium difficile* is the leading cause of antibiotic-associated diarrhoea and is a major burden to healthcare services worldwide. Fidaxomicin is a first-in-class macrocyclic antibiotic that was approved for the treatment of *C. difficile* infection (CDI) in 2011, demonstrating a narrow spectrum of activity and comparable efficacy to vancomycin in clinical trials.

Case presentation: We present the case of a patient with recurrent CDI who was non-responsive to standard treatment with metronidazole and vancomycin. The patient subsequently developed toxic megacolon, which had to be treated surgically by subtotal colectomy. Fidaxomicin at 200 mg twice daily was delivered in small-volume enemas directly to the oral part of the sigmoid colon to preserve the remaining rectosigmoid colon and improve the chances of restoring gastrointestinal tract continuity. After 11 days of local fidaxomicin therapy, diagnostic tests revealed that the patient was *C. difficile* negative and no recurrence of CDI was observed. Restoration of the gastrointestinal tract was successfully completed 5 months after hospital discharge.

Conclusion: This report describes a novel concept of local fidaxomicin delivery to the rectosigmoid colon, with an improved clinical outcome compared with metronidazole and vancomycin treatment. The study suggests that topical application of fidaxomicin may be beneficial in some CDI patients following surgical treatment for toxic megacolon.

Keywords: *Clostridium difficile*; colectomy; fidaxomicin; rectosigmoid colon; recurring.

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Introduction

Clostridium difficile is a Gram-positive, spore-forming anaerobe and is the major cause of nosocomial diarrhoea in developed countries. *C. difficile* capitalizes on disruption of the microbiota to colonize the large intestine, causing disease primarily through the action of two large toxins, toxin A (enterotoxin) and toxin B (cytotoxin) (Kuehne *et al.*, 2010; Lyras *et al.*, 2009; Poxton *et al.*, 2001). The clinical burden of *C. difficile* infection (CDI) is compounded by the fact that up to 25 % of patients suffer recurrent disease within 30 days of the first episode (Louie *et al.*, 2011; Lowy *et al.*, 2010), and the European Society of Clinical Microbiology and Infectious Diseases recognises that CDI recurrence is a major challenge to clinical practice (Bauer *et al.*, 2009). Fidaxomicin is a novel macrocyclic antibiotic with targeted bactericidal activity against *C. difficile* and limited activity

against commensal microbiota (Astellas Pharma Europe Ltd, 2011). Systemic absorption of fidaxomicin is low, enabling it to act locally at the gut level with a minimal risk of adverse events (Shue *et al.*, 2008). This report describes the local application of fidaxomicin in a patient with subtotal colectomy following recurrent CDI that was non-responsive to metronidazole and vancomycin. The study was carried out with the full informed consent of the patient.

Case report

A 74-year-old patient was admitted to the orthopaedic ward for elective knee replacement as a result of arthrosis. Her medical history was hypertension, type II diabetes (treated with oral antidiabetics) and autoimmune hypothyreosis. Pre-operative urea and creatinine levels were 5.3 mmol l⁻¹ and 67.2 µmol l⁻¹, respectively. A total knee replacement was performed under general anaesthesia with cefazolin administered as antibiotic prophylaxis (first

Abbreviations: CDI, *Clostridium difficile* infection; GDH, glutamate dehydrogenase; ICU, intensive care unit.

dose 30 min before operation and then continued therapy for 24 h post-operation) and amoxicillin was administered to treat a localized skin infection near to the surgical site. On the second post-operative day, the patient developed diarrhoea, and a stool analysis (C. Diff Quik Chek Complete; Techlab) was found to be positive for *C. difficile* glutamate dehydrogenase (GDH), toxin A and toxin B. By day 4, her clinical state had worsened with a progressive rise of infectious markers (C-reactive protein, 525 mg l^{-1} ; procalcitonin, $10.54 \text{ } \mu\text{g l}^{-1}$) and decreased kidney function (urea, 23.7 mmol l^{-1} ; creatinin, $370.8 \text{ } \mu\text{mol l}^{-1}$). Lactate levels were normal and the patient was afebrile.

The patient was transferred to an intensive care unit (ICU) and a bowel ultrasound revealed a thickened bowel wall to 10 mm with a collapsed colon lumen (known as pancolitis). A colonoscopy (up to hepatic flexure) was performed and indicated severe colitis. Upon carrying out a biopsy, non-specific inflammatory changes were observed without cryptic formed abscesses. Noradrenalin treatment was commenced at a dose of $0.15 \text{ } \mu\text{g kg}^{-1} \text{ min}^{-1}$ to treat the further progression of septic shock and antibiotic treatment was administered to treat CDI (oral vancomycin 125 mg four times daily and intravenous metronidazole 500 mg three times daily). On day 4 post-admission, leukocyte counts peaked at $23.4 \times 10^6 \text{ l}^{-1}$ before gradually normalizing by day 11, as did the C-reactive protein levels (day 2, 186 mg l^{-1} ; day 8, 33 mg l^{-1}). Serum creatinine levels normalized by day 8 post-admission, but diarrhoea continued at the rate of 6–10 stools day^{-1} . On days 11, 20 and 22, *C. difficile* GDH and toxin tests were negative and antibiotic therapy was discontinued on day 15. However, 8 days following ICU admission, heparin-induced thrombocytopenia was diagnosed. As a result, fondaparinux was started, and amikacin was administered 2 days later, for 4 days, to treat a urinary tract infection.

On day 27, sepsis again developed and a urinary tract infection was confirmed. A CT scan of the thorax and abdomen was performed and pneumonia was discounted, but bowel thickening was again observed. Due to the

urinary tract infection and a suspicion of knee endoprosthesis infection, piperacillin/tazobactam treatment was started. Vancomycin and metronidazole were restarted due to suspicion of CDI recurrence. On day 29, toxic megacolon was confirmed by a further colonoscopy (Fig. 1a) and subsequent surgery was indicated. A subtotal colectomy with terminal ileostomy and sigmoidostomy was carried out, and the abdominal cavity was left open. A cholecystectomy was performed due to phlegmonous gall bladder observed during the operation. Recurrence of CDI was confirmed through *C. difficile* antigen and toxin tests. On completion of a bioptic sample of colon tissue, pseudomembranous colitis was revealed with reactive fibrin plaques and incipient necrosis of the colon. Piperacillin/tazobactam was continued and vancomycin at 500 mg four times daily was added via a nasogastric tube. Vancomycin (500 mg diluted in 100 ml normal saline) was also added internally through the sigmoideostomy and rectum. Intravenous fluconazole at 400 mg was added to therapy following positive identification of *Candida albicans* in a stool sample.

On day 31, closure of the abdominal cavity was performed, and on day 33 a second-look colonoscopy showed continuous circular pseudomembranous colitis (Fig. 1b). Intravenous antibiotics and antifungals were discontinued on day 36 due to elevated liver enzyme levels. On day 39, the colonoscopy was repeated and indicated that only 30 % of the mucosa had healed. Diagnostic tests revealed the presence of *C. difficile* GDH and toxin in the rectosigmoid colon and PCR-ribotyping identified a *C. difficile* stem subtype 'like 027' (a PCR-ribotype 176 *C. difficile* strain was confirmed in other patients who were in contact with our patient). At this phase of treatment, the patient was showing signs of malnutrition and weak muscular strength and was unable to rehabilitate following knee replacement. Consequently, resection of the remaining colon was considered; however, this solution would have removed the possibility of restoring gastrointestinal continuity. Therefore, on day 39, fidaxomicin therapy was administered locally as a final solution. Fidaxomicin at 200 mg twice daily was delivered in small-volume enemas

Fig. 1. Colonoscopy performed up to hepatic flexure showing toxic megacolon at day 29 post-admission (a), continuous circular pseudomembranous colitis at day 33 post-admission (b) and revitalized mucosa of the rectosigmoid colon without any signs of inflammation following local fidaxomicin application at day 50 post-admission (c).

directly to the oral part of the sigmoid colon. The enema composition was prepared by dilution of a fidaxomicin 200 mg tablet in 100 ml normal saline and was applied via infusion set for 30 min for each dose. At this time, metronidazole, fluconazole and vancomycin (local sigmoid colon dose) were discontinued. On day 45, vancomycin via the nasogastric tube was discontinued. On day 50, a third-look colonoscopy was carried out, which demonstrated revitalized mucosa of the rectosigmoid colon without any signs of inflammation (Fig. 1c). Diagnostic tests were negative for *C. difficile* GDH and toxin; therefore, fidaxomicin was discontinued. On day 52, the patient was discharged from the ICU and on day 65 the patient was discharged home. A control colonoscopy was performed in an outpatient setting and showed the mucosa without any inflammation; restoration of the gastrointestinal tract was successfully completed 5 months after hospital discharge.

Discussion

In this case, locally applied fidaxomicin was used successfully to treat a 74-year-old patient with recurrent CDI and subtotal colectomy following a total knee replacement. Initially, CDI was adequately treated with a combination of metronidazole and vancomycin for 15 days. However, 11 days after discontinuation of antibiotics, CDI recurrence was noted and a colonoscopy indicated toxic megacolon that required subtotal colectomy. After 11 days of local fidaxomicin therapy, the patient was *C. difficile* negative and there was no recurrence of CDI. A recent systematic review concluded that total colectomy with end ileostomy (subtotal or total colectomy without primary anastomosis) is the preferred surgical procedure in patients with severe CDI (Bhangu *et al.*, 2012). Clinical cure of the rectosigmoid stump is essential for facilitating gastrointestinal tract restoration post-colectomy. This study describes a new concept of local fidaxomicin delivery to the rectosigmoid colon, with an improved clinical outcome compared with combined metronidazole and vancomycin treatment. The study indicates that topical application of fidaxomicin may be beneficial in some CDI patients following surgical treatment for toxic megacolon. Furthermore, because the rectosigmoid stump is safely accessible through colonoscopy, the progress of treatment can easily be monitored.

However, fidaxomicin is not currently licensed for topical administration. Therefore, further studies are necessary to demonstrate the efficacy and safety of this method of administration.

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