Tigecycline (Tygacil): Efficacy and role in the management of catastrophic intra-abdominal sepsis

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Citation

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Abstract

Tigecycline is a novel new antibiotic that has been studied and approved for the treatment of skin and soft tissue infections and intra-abdominal sepsis. However, its use in severe catastrophic intra-abdominal infections such as peritonitis secondary to ischemic/ pseudomembranous colitis and undrained liver abscesses has not been studied or reported in the literature.
We report two patients with severe intra-abdominal infections in which tigecycline was used successfully to treat a severe case of Clostridium difficile (C. difficile) associated peritonitis/ischemic bowel in septic shock and to treat another patient with a liver abscess that could not be drained.

CASE 1

A 71 year old male presented to the hospital with severe diarrhea, nausea and weakness. Three weeks prior to admission, the patient took 4 days of clindamycin, followed by 3 days of erythromycin for a tooth abscess. Upon arrival to the hospital, he was found to have a pulse of 100 beats per minute and blood pressure of 86/52 mm Hg with temperature of 98.7 F. Clinical findings were significant for severe dehydration and diffuse abdominal tenderness with mild distension. The flat plate of the abdomen showed dilated large bowel. Initial lab work revealed WBC 27,000 cu/mm3, Hgb 18 g/dl, Hct 51%, Platelets 265,000 cu/mm3, BUN 48 mg/dL, creatinine 3.8 mg/dL. The stool was positive for C.difficile.

The patient was started on intravenous fluids and oral metronidazole. Despite aggressive rehydration and electrolyte correction, he continued to deteriorate over 24 to 48 hours, eventually developing livedo reticularis and persistent hypotension. Lab work forty-eight hours after admission was as follows: WBC 48,000 cu/mm3 with 49% bands, PT 24 sec, PTT 66 sec, Fibrinogen 500 mg/ml, SGOT 341 U/L, SGPT 62 U/L, alkaline phosphatase 238 U/L, BUN 60 mg/dL, and creatinine 3.8 mg/dL. Tigecycline was started with a loading dose of 100 mg IV followed by 50 mg IV every 12 hours. In addition, he was placed on intravenous hydrocortisone and vasopressor support for the septic shock.

The abdominal distension worsened and he was taken to surgery where he was noted to have ischemic/pseudomembranous colitis consistent with toxic megacolon. A complete resection of the large bowel was performed. Initial intra-abdominal cultures were negative, but a subsequent intra-peritoneal culture, obtained during a second surgery for resection of perforated and necrotic bowel, grew Klebsiella pneumoniae which was sensitive to tigecycline. The hospitalization was complicated by disseminated intravascular coagulation and pre-renal azotemia. Eventually, the septic shock and multi-organ failure resolved and the patient was transferred to a rehabilitation facility.

CASE 2

A 67 year old man presented to the hospital with sudden onset of nausea and vomiting with black stools associated with abdominal pain 48-72 hours prior to admission. One week prior to admission, the patient had a cholecystectomy. An ultrasound showed evidence of multiple stones and a normal common bile duct with an abscess in the bed of the liver. This was confirmed with a CT scan.

On examination the patient had a temperature of 101.1 F, blood pressure of 100/78 mm Hg, pulse 98/bpm. Physical examination was significant for tenderness in the right upper quadrant without abdominal distention or rebound tenderness. Rectal examination was heme-occult positive. The rest of the examination was unremarkable.

Initial lab revealed a WBC 18,000 cu/mm^3 with 1% bands, bilirubin 1.5 mg/ml, SGOT 49 U/L, SGPT 99 U/L, BUN 29

mg/dL, and creatinine 1.0 mg/dL. He was initially started on levofloxacin but did not respond clinically for 72 hours and therefore was switched to tigecycline 100mg IV loading dose followed by 50 mg IV every 12 hours. An attempt was made to drain the abscess with CT guidance, but it could not be reached due to its location.

The patient was successfully treated with 14 days of tigecycline. Repeat CT scan of the abdomen to assess for resolution revealed a decrease in the size of the abscess with eventual resolution of the abscess. Follow up 2 months later revealed no evidence of residual abscess.

DISCUSSION

The initial selection of antimicrobial therapy for intra-abdominal and nosocomial infections is critical and requires careful consideration as inappropriate selection of antimicrobial therapy may delay clinical resolution and may result in an increased morbidity and mortality in patients. The choice of the antibiotic depends on whether this is a community or nosocomial infection and the history of bacterial resistance in the hospital and in the community. [5, 6, 8] The use of broad spectrum antibiotics (such as carbapenem monotherapy, piperacillan-tazobactam, and third or fourth generation cephalosporin's) or combination therapy (fluoroquinolones with metronidazole) can be used for severe postoperative nosocomial intraabdominal infections. [6]

Tigecycline is the first of a new class of antibiotics known as glycylcyclines, which acts by inhibiting protein synthesis at the level of the bacterial ribosome. It is a broad spectrum antibiotic with activity against gram positive, gram negative and anaerobes [1] and has been studied in the treatment of complicated skin and skin structure and complicated intra-abdominal infections (cIAI). Tigecycline currently is indicated for the treatment of adults with cIAI caused by susceptible strains of Citrobacter freundii, Enterobacter cloacae, Escherichia coli, Klebsiella oxytoca, Klebsiella pneumoniae, Enterococcus faecalis (vancomycin-susceptible isolates only), Staphylococcus aureus (methicillin-susceptible isolates only), Streptococcus anginosus group (including S. anginosus, S. intermedius, and S. constellatus), Bacteroides species, Clostridium perfringens, and Peptostreptococcus micros. [2] It has minimal to no activity against Pseudomonas species and Proteus mirabilis species.

Tigecycline is rapidly and extensively distributed and appears to have high concentrations in the following tissues: gallbladder (38-fold) lung (8.6-fold), colon (2.1-fold), lower in synovial fluid (0.58-fold) and bone (0.35-fold) relative to serum. [2] The MIC for K. pneumoniae was 1mcg/ml in the cIAI studies [9] and therefore was a good choice in patient 1. Despite this data and the clinical studies published, its efficacy and safety in certain clinical situations such as pseudomembranous associated toxic mega colon and liver abscesses has not been well documented. There has been one case of MRSA associated peritonitis that was treated successfully with tigecycline in a renal transplant recipient that was recently accepted for publication. [4]

Interestingly, in the clinical trials, no patients treated with tigecycline appeared to test positive for the C. difficile toxin or developed pseudomembranous colitis. This feature may be another reason why this drug may be an attractive choice in patients with sepsis syndrome and trans-colonic sepsis in which antimicrobial therapy may be needed. For patients with serious intra-abdominal infections, such as liver abscesses, the optimal source control of the infection would include drainage of the abscesses, debridement of necrotic tissue and definitive measures to control a source of ongoing microbial contamination. [7] However, there may be patients in whom this may not be possible (such as patient 2) and again, tigecycline, may be an attractive choice.

In summary, tigecycline appears to be a good choice for some unusual presentations of intraabdominal infections but further clinical studies to document it efficacy will be required.

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