

Antibiotic time-lag combination therapy with fosfomycin for postoperative intra-abdominal abscesses

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Abstract The first-line treatment for intra-abdominal abscess is source control. Sometimes, however, source control is too invasive for relatively small abscesses and is not feasible due to the risk of injury to some organs. Based on reports that fosfomycin (FOM) can break up biofilms to enhance the permeability of other antibiotics, we investigated the FOM time-lag combination therapy (FOM-TLCT). We enrolled 114 patients who had intra-abdominal abscess after gastrointestinal surgery and examined the efficacy of FOM-TLCT using the same therapeutic antibiotic (TA) as that which had been used previously, but had proven ineffective, at the same dose schedule. The efficacy endpoint determination was carried out as follows: among the systemic inflammatory response syndrome (SIRS)-positive cases, even after administration of TA, excellent outcome was defined as SIRS negative within 7 days of FOM-TLCT with TA without the need for other treatment, including other antibiotics or drainage. Of the 114 patients enrolled, 104 cases (SIRS positive 73; SIRS negative 31) were assessed. Ten patients were excluded; four had received TA at higher doses, three had received different TAs, and three were considered to have bacteria resistant to TAs. Among these patients, 86.3% (63/73) of the SIRS-positive cases were classified as excellent, and 90.3% (28/31) of the SIRS-negative cases were classified as effective. In total, the efficacy rate was 87.5% (91/104). The total

no-response rates were 12.5% (13/104). FOM-TLCT seems to be effective for treating refractory intra-abdominal abscess.

Keywords Intra-abdominal abscess · Surgical-site infection · Fosfomycin · Time-lag therapy

Introduction

Intra-abdominal abscesses are a major complication of gastrointestinal surgery, and many of the causative organisms have been found to be resistant to treatment. Common causes are suture failure (anastomotic leakage) and pancreatic juice fistulas, and they sometimes progress to major complications. The primary method of treating intra-abdominal abscesses is source control, and when drainage from the body surface guided by abdominal ultrasonography or computed tomography (CT) is successful, favorable results can be expected. However, sometimes, CT or abdominal ultrasonography shows that the abscess is not very large, and reoperation would be too invasive, or that even with interventional radiology (IVR) guided by abdominal ultrasonography, drainage would be impossible because of the risk of damaging the intestine or other organs. In such cases, there may be no other choice but to rely on antibiotic therapy, but even when administered in sufficient doses, the efficacy of antibiotics that have activity against the causative organism of the abscess is sometimes inadequate. It is suspected that the cause of antibiotic therapy failure is a thick capsule that has formed around the abscess, preventing the antibiotic to penetrate to the abscess. Kumon et al. [1] indicated that fosfomycin (FOM), and antibiotic widely used in Japan, breaks down biofilms and increases permeability to antibiotics, and they advocate time-lag combination therapy (FOM-TLCT) in

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which FOM is administered 1 h before antibiotic administration. In this study, we assessed treatment of intra-abdominal abscesses by FOM-TLCT.

Patients and methods

Study participants were 114 patients found to have an intra-abdominal abscess by CT or abdominal ultrasonography after gastrointestinal surgery in our department during the 12-year period from April 1997 to March 2009 and who received FOM-TLCT. All were inpatients in whom a complete cure was not achieved despite therapy with antibiotics to which the bacterial isolates obtained from the abscess by drainage or reoperation exhibited susceptibility. We used FOM-TLCT to treat these patients, prescribing the same drugs, doses, and dose schedules that had been ineffective up to that point, and assessed the efficacy of FOM-TLCT. Inclusion criteria were: (1) patients with an intra-abdominal abscess that had developed after gastrointestinal surgery and in which the abscess had been confirmed by CT, ultrasonography, or a contrast study of the gastrointestinal tract; (2) patients in whom the infectious signs failed to resolve despite treatment with first- and second-line antimicrobial drugs, drainage, or even reoperation; and (3) patients in whom an antibiotic to which the isolates from the abscess showed susceptibility was administered for at least 3 days according to an adequate dose schedule. Abscess size, number of abscesses, and thickness of the abscess wall were not taken into consideration when selecting patients. The exclusion criteria were: (1) patients in whom the antibiotic was changed during administration of FOM-TLCT and patients whose dose and the method of administration were changed; (2) patients in whom drainage or reoperation had been performed within 3 days before the start of FOM-TLCT administration; (3) patients in whom bacteria resistant to the drug being used for treatment were newly isolated during administration of FOM-TLCT; and (4) patients in whom the duration of FOM-TLCT was <3 days.

FOM was administered by dissolving 2.0 in a suitable infusion preparation and infusing it over a period of 30–60 min. Administration of the same antibiotic as used to treat the abscess up to that point was started 1 h after completion of the FOM infusion, and it was administered irrespective of whether the isolate exhibited susceptibility to FOM. If the antibiotic was administered once daily or twice daily, FOM was administered before each dose. If the antibiotic was administered three or four times daily, FOM was administered 1 h before the first and third doses.

We assessed these patients in regard to age, sex, disease for which surgery was performed, surgical procedure,

whether suture failure occurred, antibiotic, duration of treatment, dose before treatment with FOM, bacteria isolated from the abscess, interval between surgery and FOM-TLCT, duration and efficacy of treatment with the antibiotic after administration of FOM, and adverse effects associated with TLCT. In patients who had an intra-abdominal abscess, a white blood cell (WBC) count $\geq 11,000$, and a body temperature $\geq 37.4^{\circ}\text{C}$ [systemic inflammatory response syndrome (SIRS)-positive cases] who failed to convert to SIRS negative despite ≥ 3 days of treatment with the antibiotic for an isolate from the abscess that was susceptible to the agent, efficacy was judged to be “excellent” when FOM-TLCT and treatment with the same antibiotic was continued and within 7 days and the WBC decreased to $\leq 9,000$, body temperature was $\leq 37.0^{\circ}\text{C}$, and there was no subsequent need for treatment of the abscess with other antibiotic therapy or surgical drainage. On the other hand, in patients who had an intra-abdominal abscess, a WBC count $\geq 11,000$, and a body temperature $\geq 37.4^{\circ}\text{C}$ in whom SIRS converted to negative in response ≥ 3 days of treatment with an antibiotic to which the isolate from the abscess exhibited susceptibility (non-SIRS cases), cases in which treatment with the same antibiotic was continued together with FOM-TLCT and within 7 days of the start of FOM administration the WBC had decreased $\leq 9,000$, body temperature $\leq 37.0^{\circ}\text{C}$, and there was no subsequent need for treatment of the abscess with another antibiotic or surgical drainage, efficacy was judged to “effective.” All cases were followed up for at least 30 days after the start of FOM-TLCT, and a final evaluation was made.

Among cases other than those described above, those in which the antibiotic was administered together with FOM-TLCT but there was no alleviation of the manifestations of infection, and drainage or reoperation was necessary during FOM-TLCT or after the completion the FOM-TLCT, efficacy was evaluated as “ineffective.” Cases in which the antibiotic used in combination with FOM-TLCT was changed or another drug was added, cases in which the dose or dose schedule was changed even though the same antibiotic was being used for treatment, cases in which bacteria resistant to the antibiotic were newly isolated, and cases in which there was another infection besides the intra-abdominal abscess were excluded from the study.

According to the criteria for antibiotic therapy during the perioperative period in our department, for 1–3 days beginning immediately before the start of the operation and including the day of the operation, cefazolin is administered to prevent postoperative infection after upper gastrointestinal tract surgery (esophagus, stomach, gall bladder). Cefotiam is administered beginning immediately before the start of lower gastrointestinal tract surgery and liver or pancreatic surgery, and if there are no signs of postoperative infection on postoperative day (POD) 3, administration of the

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