EFFECTS OF OCTREOTIDE PHARMACOTHERAPY IN THE TREATMENT OF COMPLICATED PERFORATION OF RETROPERITONEAL DUODENAL ULCER

Skuteczność farmakoterapii oktreotydem w leczeniu umiejscowionego zaotrzewnowo wrzodu dwunastnicy powikłanego perforacją

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Abstract

Duodenal ulcer is a defect in the mucosa. The main aetiological factors are *H. pylori* infection, nonsteroidal anti-inflammatory drugs, genetic factors, and nicotinism. Statistics confirm that perforation is a significant and potentially life-threatening ulcer complication in the Polish population. Octreotide is a somatostatin derivative that works by inhibiting the release of proteins of the gastrointestinal-pancreatic system. It is indicated in acromegaly, hormonally active gastrointestinal tumours, and oesophageal variceal bleeding. It can be used to reduce bile secretion and slow down gallbladder motility. The material for this review paper was a case of duodenal perforation in a woman aged 63 years. Octreotide used in the treatment of a difficult-to-heal anastomosis improved the patient's local and general condition, and led to the closure of the anastomosis. Despite the significant number of circumstances leading to the patient's life-threatening condition in the course of the perforation, there were also factors that positively influenced the treatment outcome. The most important of these was the use of octreotide to increase the chances of healing of the intestinal-intestinal anastomosis in the area of influence of digestive enzymes. The conclusions drawn from this case suggest that octreotide can be used in the treatment of non-healing, properly performed gastrointestinal anastomoses. More effective prophylaxis, early diagnosis of peptic ulcer disease, and increasing access to endoscopy are known to reduce the number of perforation cases. Importantly, there are cases of perforations that can be life-threatening for the patient even in the course of anastomotic dissections of properly performed surgical procedures. Octreotide should be considered in the management of complicated and extreme perforations. This paper describes the possibility of using octreotide as a pharmacotherapy to increase the chances of gastrointestinal anastomosis healing in cases involving complicated duodenal perforations.

Streszczenie

Wrzód dwunastnicy stanowi miejscowy ubytek w błonie śluzowej pokrywającej wnętrze tego odcinka przewodu pokarmowego. Do głównych przyczyn choroby wrzodowej dwunastnicy zalicza się zakażenie bakterią *H. pylori*, stosowanie niesteroidowych leków przeciwzapalnych, predyspozycje genetyczne oraz palenie tytoniu. Dane statystyczne wskazują, że w polskiej populacji ciężkim i potencjalnie zagrażającym życiu powikłaniem choroby wrzodowej jest perforacja wrzodu. Oktreotyd jest pochodną somatostatyny. Działa poprzez hamowanie uwalniania peptydów wytwarzanych przez wewnątrzwydzielniczy układ żołądkowo-jelitowo-trzustkowy. Lek ten jest wykorzystywany w terapii akromegalii, hormonalnie czynnych guzów przewodu pokarmowego oraz krwawień z żylaków przełyku. Może być również stosowany w celu zmniejszenia wydzielania żółci i spowolnienia motoryki pęcherzyka żółciowego. Punktem wyjścia dla poniższej pracy przeglądowej był przypadek perforacji wrzodu dwunastnicy u 63-letniej pacjentki. W leczeniu trudno gojącego się zespolenia zastosowano oktreotyd. Lek ten poprawił stan miejscowy i ogólny pacjentki, a także przyczynił się do zamknięcia zespolenia. Pomimo szeregu czynników, które doprowadziły do stanu zagrożenia życia w przebiegu perforacji, odnotowano także okoliczności o korzystnym wpływie na końcowy wynik leczenia. Najważniejszym czynnikiem okazało się wdrożenie leczenia oktreotydem, aby zwiększyć szanse na wygojenie zespolenia jelitowo-jelitowego w obszarze oddziaływania enzymów trawiennych. Opisany przypadek wskazuje na zasadność stosowania oktreotydu w leczeniu prawidłowo wykonanych, ale trudno gojących się zespoleń żołądkowo-jelitowych. Wśród czynników, które przyczyniają się do zmniejszenia liczby przypadków perforacji, należy wymienić skuteczną profilaktykę, wczesne wykrywanie choroby wrzodowej oraz dostęp do badań endoskopowych. Należy jednak zaznaczyć, że przypadki perforacji stanowiących zagrożenie dla życia pacjenta mogą wystąpić nawet przy prawidłowo przeprowadzonym zabiegu zespolenia. W leczeniu złożonych, ciężkich perforacji warto rozważyć wdrożenie oktreotydu. W pracy opisano możliwość zastosowania oktreotydu w ramach farmakoterapii zwiększającej szanse na wygojenie zespolenia żołądkowo-jelitowego u pacjentów z perforacją dwunastnicy.

Keywords: ulcer; octreotide; duodenum; perforation

Słowa kluczowe: wrzód; oktreotyd; dwunastnica; perforacja

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Introduction

Both stomach and duodenum ulcers are mucosal defects, penetrating beyond the *muscularis lamina* with inflammatory infiltration and necrosis, limited in nature [1]. The main aetiological factors include *H. pylori* infection and non-steroidal anti-inflammatory drugs (NSAIDs). In addition, certain genetic factors, such as blood type 0, or the gene-dependent number of lining cells in the stomach and their sensitivity to gastrin, are known to promote peptic ulcer disease.

Cigarette smoking is an important factor hindering ulcer healing and increasing the incidence of ulcer disease [1]. The prevalence of duodenal ulcer disease is approximately 55 000 in the adult Polish population, with a three-fold predominance in men [1]. One of its main complications, besides haemorrhage and pyloric stenosis, is ulcer perforation. It affects about 2–7% of patients with peptic ulcer disease [2], with the mortality rate varying between 4–40% [3].

Octreotide is a synthetic somatostatin derivative which, while exhibiting similar properties, demonstrates a longer (1.5-hour) half-life in the blood. The action of this drug involves inhibiting the release of serotonin, the growth hormone, and the proteins of the gastroenteropancreatic (GEP) system [4]. Octreotide is often prescribed in acromegaly, in hormonally active gastrointestinal tumours, and in cases of oesophageal variceal bleeding. Unlike other somatostatin analogues, octreotide is administered in pre- and post-operative prophylaxis in patients referred for surgical treatment of pancreatitis. In addition, when used in single doses, it may decrease bile secretion and suppress gallbladder motility. Possible side effects of octreotide treatment may include pain at the administration site, diarrhoea, gallstones or hyperglycaemia. The dosage used for preventing complications after pancreatic surgery is 0.1 mg 3 ×/d for 7 days [5, 6].

Case report

A female patient, I.P., aged 63 years, was admitted to the Department of General Surgery at the Olesno Complex of Health Care Centres (Case Record No. 3432/2022) with suspected perforation of gastric or duodenal ulcer. On 4 September 2022, she presented to the Emergency Department of the Olesno Hospital with epigastric pain that had persisted for several days. In the course of diagnostics, an abdominal CT scan was performed, suggesting stomach or duodenum perforation. On the same day, the patient was referred and admitted to the Department of General Surgery, where L5-S1 spinal discopathy, the use of NSAID painkillers, type 2 diabetes mellitus, and hypertension in history were found. The patient denied nicotinism. On admission, her general condition was average. The patient reported rather severe pain; the heart rate was steady (100 bpm) and the blood pressure was 85/55 mmHg. On physical examination, there was abdominal pain in the epigastrium and umbilical region, peritoneal symptoms in the epigastrium and mid-abdomen on the right side, and an umbilical hernia. Laboratory tests yielded the following results: CRP 98.45 mg/L, D-dimers >4.00 µg FEU/mL, blood group – 0 RhD positive, GFR 33 mL/min/1.73 m^2, Troponin T 28.64 ng/L. The patient was urgently scheduled for surgery. Hydration, thromboprophylaxis, and antibiotic therapy with Biofuroxime 3 × 1.5 g/d and Metronidazole 3 × 0.5 g/d were ordered. A laparotomy was carried out, revealing purulent contents in the peritoneal cavity, sampled for bacteriological examination. Some yellow-coloured contents were visualised in the subhepatic area. An inflammatory infiltrate was found, involving the hepatoduodenal and hepatogastric ligaments. After evacuation of the duodenal contents, an oval perforation, about 20 mm in diameter, was observed in the posterior-superior wall of the duodenum. The attempt to close the hole with sutures was abandoned because of its size, the inflammatory infiltration, and altered anatomical relationships. The rather challenging stump of the duodenum was closed by the Nissen method. Drains were positioned around the stump: one was inserted into the epigastrium, while two other were placed in the mid-abdomen. Subsequently, the stomach was resected by the Billroth II method, followed by Braun's enterostomy. A micro-jejunostomy was guided through an incision in the wall of the jejunum for enteral nutrition. In addition, the patient was fitted with a gastric probe and transferred to the Acute Intensive Care Unit (AICU) for further treatment.

There, the patient was diagnosed with acute respiratory failure, hypovolaemic shock, peritonitis, obesity and, upon a detailed examination of her history, with nicotinism. Blood pressure during norepinephrine infusions was 90/40 mmHg and the heart rate was 80/min. Antithrombotic prophylaxis, analgosedation, and symptomatic treatment were continued. On admission to the AICU, the following were noted: hypoalbuminaemia 2.56 g/dL, hypoproteinaemia 4.18 g/dL, and procalcitonin 26.01 ng/mL. The abdominal culture revealed the presence of *C. albicans*. During the patient's stay at the AICU, she was fed parenterally with SmofKabiven, 986 mL/d, Cernevit, 1 amp/d, and Supliven 1 amp/d. The initial empirical antibiotic therapy was changed to Vancomycin, 1 g/d, Amikacin, 1.5 g/d, and Caspofungin, 50 mg/d. On the third postoperative day, the patient was extu-

bated following an improvement in her general condition. The drains were retained throughout the patient's stay at the Unit; serous-purulent contents were removed through the drain inserted into the anastomotic area. After surgical consultation, a 5% glucose solution was ordered for administration through the jejunostomy. It was recommended that the drains be left in place for the risk of wound dehiscence in the sutured duodenum. The treatment was continued until 11 September 2022, when the patient was surgically consulted again. A small amount of bile-coloured contents was found to flow from the duodenal stump drain. Similar contents were aspirated through the probe from the gastric stump. The duodenal stump was found to be leaking, and a conservative treatment was recommended, with extra- and enteral nutrition. Simultaneously, water-electrolyte and acid-base imbalances were corrected, achieving cardiovascular stabilisation. The results of the follow-up examinations, carried out on 11 September 2022, were as follows: hypoalbuminaemia 2.16 g/dL, total protein 4.40 g/dL, CRP 97.82 mg/L, D-dimers 2.97 µg FEU/mL, GFR >60 mL/min/1.73 m^2, WBC 20,000/µL, RBC 3.33 million/µL, HGB 10.3 g/dL, NtproBNP 965.5 pg/mL, Procalcitonin 1.87 ng/mL. After surgical consultation, it was decided to transfer the patient to the Department of General Surgery on 11 September 2022.

After the patient was transferred to the Department of General Surgery, the conservative management was maintained. The antibiotic therapy, extra- and enteral nutrition, and symptomatic treatment were carried on. The antibiotic therapy and the treatment with Caspofungin were terminated on 12 September 2022. Fluconazole, 20 mg 1×/d iv, was initiated. On 14 September 2022, taking into account the patient's stable condition, she was gradually tilted to the upright position. After the passing of several loose stools on 17 September 2022, the patient was diagnosed for infection with *C. difficile*, but an immunoenzymatic test was negative. The control of the contents, guided by the drains inserted into the duodenal stump area, was continued. The drains systematically discharged bile contents throughout the period of hospitalisation. On 19 September 2022, an intestinal anastomosis leak test was performed with an orally administered contrast agent, confirming a post-operative leakage in the gastrointestinal tract; for that reason, enteral feeding was discontinued. On 21 September 2022, the patient's condition was described as moderate, with the dressing soaked with the contents coming out from the forming fistula. On the subsequent day, there was an episode of blood pressure rise, corrected by the i.v. administration of Tachyben, 12.5 mg. In addition, it was necessary to change the dressings due to profuse exudate. On 23 September 2022, the patient's condition worsened, with an increased leakage of purulent contents from the surgical wound and in the area of the nutrient fistula. The patient was then scheduled for relaparotomy due to a suspected intestinal fistula, and the procedure was performed immediately. During the surgery, multiple intestinal adhesions were released, and the cavity of the subdiaphragmatic abscess on the left side was opened and rinsed. The gastrointestinal anastomosis and the Braun anastomosis were tight, while bile contents were leaking from the duodenal stump. Drains were placed in the subdiaphragmatic abscess cavity, the opening in the duodenal stump, the stump area, and in the pouch of Douglas. Intraoperative laboratory results were as follows: hypoalbuminaemia 2.88 g/dL, total protein 5.38 g/dL, CRP 188.97 mg/L, GFR >60 mL/min/1.73 m^2, WBC 4100/µL, RBC 2.75 million/µL, HGB 8.3 g/dL, and Procalcitonin 0.35 ng/mL. After the procedure, the patient was transferred to the AICU for further treatment.

The patient's condition in the AICU was severe for 20 days. At that time, the prognosis was unfavourable, also because of a range of disadvantageous factors including the patient's age, co-morbidities, and perforation size, increasing the total risk of death to above 30% [7].

On 26 September 2022, the patient was operated twice, due to anastomotic failure. On 28 September 2022, after a surgical consultation, the patient underwent lavage and drainage of the peritoneal cavity, and a VAC dressing was applied, due to drainage failure. Another procedure took place on 1 October 2022 for suspected faecal peritonitis. The micro-jejunostomy was removed for leakage at the insertion site; in addition, numerous adhesions were released and a left-sided subdiaphragmatic abscess was removed. A significant degree of biliary infiltration was found in the duodenal stump area. During subsequent laparotomies, carried out on 5 and 7 October 2022, a significant degree of biliary infiltration was identified, and individual additional sutures were used to close anastomotic leaks, together with a new drain placed in the duodenal stump. However, the effects of these procedures were not satisfactory at all.

The leakage of gastrointestinal contents into the peritoneal cavity could not be contained. In addition to the leakage of the duodenal stump, a fistula persisted at the site of the gastrointestinal anastomosis.

The case was consulted remotely with the staff at the Department of Gastrointestinal Surgery, where it was considered as extremely challenging. However, a revision surgery was recommended to create a new gastrointestinal anastomosis. The patient was reoperated to precisely locate the leaks from the gastrointestinal anastomosis and the duodenal stump. Due to limited experience, the initial plan to perform a new anastomosis was abandoned, and a conservative treatment with octreotide was implemented instead. Octreotide was started, as recommended, at a dose of 250 µg in a bolus, followed by 250 µg/hour on the first day, then 3 mg/day for five subsequent days, and then at the dose of 1.5 mg/day. The patient's condition began to improve gradually after octreotide was added. The outflow volumes from the drains were found to be decreasing. On 20 October 2022, the patient was transferred to the Department of General Surgery for treatment continuation. The patient's test results in the follow-up examinations prior to the transfer were as follows: CRP 30.98 mg/L, WBC 6400/µL, RBC 3.03 million/µL, HGB 9.2 g/dL, Procalcitonin 0.15 ng/mL.

During the patient's stay at the Department of General Surgery, the prescribed care regimen was continued according to the established schedule. Vital parameters, wound healing, and drainage were monitored. Since the amount of contents from the drains was gradually de-

creasing, more drains could be removed. Octreotide was administered at a dose of 1.5 g per day until 7 October 2022. The patient's general condition improved successively with each day, and effective oral nutrition was started on 29 October 2022.

The patient was discharged home on 11 November 2022 in good general condition, with recommended follow-up at the General Surgery Outpatient Clinic. The patient was hospitalised for a total of 69 days, during which she was operated on six times.

Discussion

Ulcer perforation in the upper gastrointestinal tract is one of more dramatic and dangerous complications of reckless NSAID use [8]. Prophylactic therapy with proton pump inhibitors is a legitimate means of preventing this complication in chronic NSAID users [9]. While preventive therapy is recommended, a lack of information or non-compliance among some patients can result in serious complications, including life-threatening gastrointestinal perforation. In case of perforation in the course of peptic ulcer disease, the recommended management is surgery by Billroth II subtotal gastrectomy [10]. The procedure was performed in our patient with a subsequent hospitalisation for individual treatment, along with recommended dietary and lifestyle changes [11]. The surgical procedure and pharmacotherapy were in line with the current medical knowledge, but managing leaking anastomoses proved to be a challenging problem. Despite adhering to good medical practice, both in surgery and in post-operative care, the patient's condition seriously deteriorated. The diagnosed inflammation with exacerbating mechanisms (a direct impact and amount of digestive enzymes) was regarded as the main failure factor. Treatment with octreotide was selected, even though the surgical option proposed by staff at the Department of Gastrointestinal Surgery, i.e. 'new' gastrointestinal anastomosis, seemed the most appropriate approach. Nevertheless, the medical team, fearing other failures and risks, decided to administer octreotide, taking into consideration the potential trade-off between a probably lower efficacy of the applied pharmacotherapy and the safety of the patient. The goal of optimal conditions for duodenal healing was thus met. After a 69-day hospitalisation, the patient could be discharged home.

Summing up, the main factors responsible for the patient's life-threatening condition included:

- the use of NSAIDs without proper medical supervision and the lack of prophylaxis with proton pump inhibitors during analgesic therapy,
- nicotinism,
- genetic conditions, including RhD positive blood type 0,
- the size and location of the perforated ulcer.

The factors which led to the successful outcome included:

- proper selection and execution of the surgical technique and provision of post-operative care in line with good medical practice,
- close cooperation of the medical personnel with clinical consultants,
- innovative use of octreotide in line with postprandial syndrome treatment regimens.

Conclusions

- The discussed case suggests that octreotide can be considered for the management of hard-to-heal anastomoses in the gastrointestinal tract especially in the areas impacted by digestive enzymes that may increase inflammatory processes.
- A more effective prophylaxis, an early diagnosis of peptic ulcer disease, and increased access to endoscopy help reduce the incidence of perforation with such a dramatic course. Still, serious complications of perforation do happen, including those that may put the patient at risk of death not only as a result of bleeding, but also in the course of anastomotic dissections of otherwise properly performed surgical procedures.
- One of the key conditions for the successful treatment of gastrointestinal fistulas is proper nutrition and control of the patient's protein and albumin levels throughout the treatment period.
- The course of treatment documented above implies that octreotide can be used with positive results in cases of complicated and extremely difficult perforations.

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