We present a case of a patient suffering from severe acute pancreatitis who underwent double treatment with recombinant human activated protein C. The first administration occurred while the patient was in shock secondary to severe acute pancreatitis (not complicated by pancreatic necrosis bacterial contamination). The second administration occurred while the patient was in septic shock secondary to an iatrogenic complication, which developed in convalescent period.

**Key words:** pancreatitis, shock, recombinant human activated protein C
tomy in 2003). Fluid density in CT was 5-10 HU (Hounsfield Units) indicating its effusive character.

While assessing the patient’s condition upon admission to the ICU, respiratory distress requiring mechanical ventilation at a FiO$_2$ of 1.0 was observed. Chest X-ray showed an effusion in the left pleural cavity and negligible atelectasis ipsilaterally. The patient was hemodynamically unstable and required high doses of catecholamines (dobutamine 25-30 μg/kg/min and norepinephrine 1.3-1.5 μg/kg/min) and massive fluid infusion: 8200 mL during the first 24 hours. Despite such therapy, it was difficult to achieve a mean arterial pressure (MAP) higher than 40-50 mm Hg. Anuria persisted.

The rapid worsening of blood chemical parameters was noted: hyperglycemia 47 mmol/L (382 mg%) persisted despite insulin administration, blood creatinine increased to 230 mmol/L (2.6 mg/dL) (in consecutive days even up to 495 mMol/L [5-6 mg/dL]), urea increased to 15.4 mMol/L (93 mg/dL), total bilirubin increased to 77 mMol/L (4.5 mg/dL), hyperkalemia at 6.2 mMol/L, and metabolic acidosis at a pH of 7.21. Significant disorders in the blood coagulation system were observed: a sudden decrease in the number of platelets from 135 x 10$^3$/μL to 50 x 10$^3$/μL, AT III level of 35%, D-dimer levels increased 6 fold, and the APTT doubled. The white blood cell count was within the normal range, amylase was 759 IU, cholesterol was 6.64 mMol/L (250 mg/dL), triglycerides were 14.7 mMol/L (1.279 mg/dL), CRP was 26.7 mg/dL, and Ca was 1.8 mMol/L (7.2 mg/dL). The patient’s condition achieved a score of 29 in the APACHE II scale.

Antibiotics (meropenem and fluconazole) were initiated. Pantoprazole and hydrocortisone (0.18 mg/kg/h) were administered to increase catecholamine activity. Despite the intensive care, the patient’s condition worsened. He was hemodynamically unstable. Mechanical ventilation at a FiO$_2$ of 1.0 provided oxygen pressure of only 8 kPa (60 mm Hg). PEEP greater than 5 cm H$_2$O could not be applied due to hypotension.

As the symptoms of shock developed with accompanying blood coagulation disorders, we decided to administer recombinant human activated protein C drotrecogin alfa (activated), Xigris® 14 hours following the patient’s admission to the ICU. The drug was administered at a dose of 24 μg/kg/h for 96 hours (total dose 230.4 mg). AT III rose to 61% and platelets decreased to 27 x 10$^3$/μL within the first 24 hours of therapy. FiO$_2$ was reduced to 0.8, AT III increased to 66%, normalization of APTT, and platelets of 33 x 10$^3$/μL were noted on the second day of therapy. The dose of norepinephrine necessary for the stabilization of blood circulation was decreased to 0.6 μg/kg/h. On the third day of therapy with activated protein C, further increases in AT III to 81% were achieved. FiO$_2$ was reduced to 0.6. On the fourth day, platelets increased to 41 x 10$^3$/μL, AT III to 89% and the FiO$_2$ was reduced to 0.5. Essential coagulation indices normalized, except D-dimers. Their elevated levels persisted up until the eighteenth day.

On the third day of treatment in the ICU, continuous renal replacing therapy through a catheter introduced to the right subclavian vein was conducted. Four consecutive hemodialysis sessions were performed following an improvement in circulatory system efficiency. Normal renal functioning returned on the 21st day of therapy, following polyuria. The bilirubin level normalized on the ninth day. Low catecholamines doses (0.1-0.2 μg/kg/min norepinephrine and 0.1-0.2 μg/kg/min dobutamine) were given on the tenth day.

The patient was extubated after 14 days of mechanical ventilation.

Multiple USG and CT scans, repeated after 13 days of treatment, did not show features of pancreatic necrosis bacterial contamination. The fluid present in the abdominal cavity, initially seen on CT, had a low density of approximately 10 HU. No gas or abscesses in both the pancreas and peritoneal cavity were seen.

On the sixth day of therapy, enteral nutrition through a nasogastric tube placed under gastrofiberoscopic guidance was reinstituted. In this period of treatment, the highest body temperature did not exceed 38°C, the white blood cell count in the first week of therapy was within the normal range, but it was slightly elevated to 13-15 x 10$^3$/μL in the second week. Repeat blood cultures were negative. CRP gradually decreased and reached normal values by the third week.

The patient was recovering so rapidly that his transfer to the Department of Gastroenterology had been planned for 29 August. However, violent chills and high fever (40°C) developed on 26 August. Respiratory distress with the need of mechanical ventilation at a FiO$_2$ of 1.0,
Recombinant human activated protein C administered twice to the same patient with shock caused by the acute pancreatitis and with septic shock as iatrogenic complication

circulatory failure with accompanying anuria and an increase in creatinine to 194 mMol/L (2.2 mg/dL) developed rapidly. An increase in WBC to 19x10³ μL, CRP to 10.6 mg/dL, total bilirubin to 56.4 mMol/L (3.3 mg/dL), and metabolic acidosis were seen. Septic shock was diagnosed. Samples of the blood for microbiological examination were collected from the peripheral vein and a central venous catheter (right subclavian vein). The catheter was eventually removed. Its tip was sent to the bacteriological laboratory for examination. The fluid from the abdominal cavity, typical of pancreatitis, was collected and also sent to the bacteriological laboratory. Fluids, catecholamines (dobutamine, norepinephrine), antibiotics (meropenem, linezolid, caspofungin, colistin), and Sandoglobulin were administered. Blood platelets increased from 250-300 x 10³ μL several days prior to this incident, decreased to 84 x 10³ μL and his APTT doubled. After 8 hours following the onset of infection, we decided to re-administer activated protein C at a dose of 24 μg/kg/96 h. The following day platelets rose to 103 x 10³ μL and reached 116 x 10³ μL on the fourth day. APTT normalized on the third day. We reduced norepinephrine from 0.6 to 0.2 μg/kg/min on the second day of therapy.

A 3-day empiric antibiotic therapy brought about a bacteriological response. 3 strains of bacteria were isolated from the peripheral blood sample, central blood sample and the catheter tip. Two of them, Proteus mirabilis and Acinetobacter baumanii were sensitive to meropenem, while the third, Enterococcus faecalis, was sensitive to linezolid. The fluid collected from the abdominal cavity proved sterile.

Diuresis stimulated with furosemide and mannitol returned on the second day of therapy. It was possible to reduce FiO₂ to 0.8 and to 0.5 on the third day. Creatinine and bilirubin levels returned to normal on the fifth day of therapy. The patient was extubated on the eighth day. The patient in a satisfactory general condition was transferred to the Department of Gastroenterology on the tenth day following the onset of septic shock.

DISCUSSION

Acute pancreatitis had a severe course in this patient. Upon admission to the ICU, SIRS with rapidly developing respiratory, circulatory, and blood coagulation impairment as well as renal and liver failure were diagnosed. This was confirmed by the APACHE score. Despite intensive therapy based on the actual guidelines (3, 4), the patient’s condition worsened rapidly and became life-threatening. Because of rapidly developing pathologies in the coagulation system and hemodynamic instability indirectly affecting the function of other organs, we decided to administer recombinant human activated protein C. The PROWESS study (2) showed that rhAPC efficacy depends on its administration time and the most rapid improvement is noted in the respiratory, circulatory, and coagulation systems. A predominant feature of the disease occurs from respiratory, circulatory and coagulation impairment. This information concerns septic shock but a similar cytokine cascade is seen in both septic shock and pancreatitis (5). Berger et al. (6) found significant increases in IL-6, IL-10, and IL1ra on the first day of acute pancreatitis. This was an infection-independent factor. There is sufficient evidence, which suggests that pancreatic necrosis was not contaminated with bacteria during the first episode. Therefore, rhAPC treatment efficacy may be related to the pathologies resulting from pancreatitis and not underlying infection.

The following elements advocate such a conclusion:

1. Time lapse from the onset of pancreatitis. Complications due to pancreatic necrosis bacterial contamination rarely occur in the first week of disease. The majority of them are seen in the second or third week (6).
2. Body temperature between 37.5°C and 38°C. Elevated body temperature in the first week depends on the cytokine-modulated inflammatory reaction, infection (7).
3. Low white blood count.
4. Negative blood and peritoneal fluid cultures.
5. Low density of the abdominal fluid and lack of other signs of pancreatic necrosis infection (gas, abscesses) on CT scans.

Recombinant human activated protein C efficacy is evidenced by rapid improvement in coagulation parameters, circulatory stabilization enabling reduction of high doses of catecholamines, improved gas exchange in the lungs enabling decreases in the inspired oxygen fraction (FiO₂) as well as restitutio ad integrum of renal and liver functions. These indicate that rhAPC protected internal organs against structural damage due to the inhibi-
tion of an excessive disseminated intravascular coagulation (DIC) and apoptosis as well as profibrinolytic and anti-inflammatory properties.

The second episode of this disease in the form of septic shock was probably a complication of catheter (dialyzing) introduction, possibly because of infected thrombus separation, which was located inside the catheter. In this case, rhAPC was used in accordance with guidelines concerning acute septic shock treatment in which rapidly increasing multiorgan failure was observed (3). The immediate start of traditional therapy, proper empiric antibiotic therapy (with additional colistin, because of possible infection with resistant to carbapenems Pseudomonas spp. strains) as well as recombinant human activated protein C administration within 8 hours following the onset of shock brought about the desired therapeutic success.

The PROWESS study, which detailed the use of recombinant human activated protein C in the treatment of severe sepsis, has showed underlying pancreatitis in 3.4% of the studied patients and 9% in the placebo group. Mortality in the rhAPC group was 13.4% relative to 24.2% in the placebo group (2).

The presented case is likely one of the first in which recombinant human activated protein C was used in the treatment of shock caused by the acute pancreatitis without underlying infection. These results advocate increasing the indications for recombinant human activated protein C use.

REFERENCES


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COMMENTARY

The clinical course of an episode of acute pancreatitis (AP) varies from a mild, transitory illness to a severe, often necrotizing form with distant organ failure and a mortality rate of 20-40% (1). Those patients with severe pancreatitis, representing about 15-20% of all patients with acute pancreatitis, need to be identified as early as possible after the onset of symptoms to facilitate intensive care treatment early in the disease process (1). The two major determinants of outcome are the severity of organ dysfunction (multi-organ dysfunction syndrome – MODS) and the extent of peripancreatic necrosis, the latter of which creates the medium for bacterial proliferation. MODS is observed early after the onset of severe AP and in some cases follows pancreatic infection.

Experimental studies on severe AP have demonstrated that inflammatory mediators play an important role in local tissue injury and the development of MODS, both at the early non-infected and late infected stages of the illness. Inflammation induces pro-inflammatory mediators, which together with endothelial damage, promote coagulation when fibrinolysis is suppressed (2). The imbalance between inflammation, coagulation and fibrinolysis results in widespread coagulopathy and microvascular thrombosis, which leads to organ hypoperfusion and dysfunction. Activated protein C (APC, dro-
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trecogin alfa, Xigris®, Eli Lilly, USA) helps the body to eliminate the clot and reduces the inflammation caused by infection; APC is an antithrombotic, profibrinolytic and an anti-inflammatory agent. Xigris® was studied in an international, multi-centre, randomized, double-blind, placebo-controlled trial (PROWESS) in 1690 patients with severe sepsis; the drug was found to reduce the 28-day mortality from 30.8% (control group) to 24.7% (study group) (3). The drug is now the only treatment approved to lower the risk of death from severe sepsis in adults with multi-organ failure. However, modulation of the coagulation cascade, while probably essential to the mode of action of APC, can lead to an increased risk of bleeding. Few studies have addressed APC use in the early stage of AP. To date there is no specific pharmacological intervention for AP. From their experimental study, Yamanel et al. (4) concluded that APC reduced the severity of pancreatic tissue histology, superinfection rates and serum markers during the course of acute necrotizing pancreatitis. Synthesis of the current knowledge on the modes of action and side-effect profiles of APC into a practical management algorithm must accept the fact that the evidence in this field is changing rapidly (4). At present there is insufficient evidence to justify the use of APC in the early stage of severe AP. In later stages, when the probability of infection is proportionately greater, it is probable that intensive care clinicians will turn to activated protein C in those patients with organ dysfunction in established AP (5).

The presented case study is the first one published indicating that APC can be successfully used both at the early non-infected stage as well as at the late stage, which is complicated by bloodstream infection sepsis in patients with severe AP. Further studies are required to confirm the safety and effectiveness of such therapy.

REFERENCES


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