Successful Treatment With Continuous Enteral Protease Inhibitor in a Patient With Severe Septic Shock


ABSTRACT

Objective. The mortality rate among patients with septic shock is high despite current therapy. We present a case of Fournier's gangrene and septic shock at 4 years post-heart transplantation that was reversed by “continuous enteral feeding” of the digestive enzyme inhibitor, gabexate mesilate. Recently, powerful pancreatic digestive proteases in the lumen of the intestine have been identified as initiators of the systemic inflammatory response. Intraluminal inhibitions of the proteases significantly attenuates intestinal damage, systemic inflammation, and multiorgan failure in experimental forms of shock but it has not been tested in man.

Methods and results. Gabexate mesilate, a synthetic digestive protease inhibitor, was continuously administered in two liters of crystalloid solution to a patient by enteral feeding during septic shock. The condition and markers for shock due to sepsis reversed in a few days.

Conclusion. This case suggested that “enteral” digestive protease inhibition may decrease and even reverse the sequelae of shock and sepsis.

T he incidence of complications after transplantation is at least 50% with a mortality rate of septic shock up to 30%. If the condition is accompanied by elevated levels of pancreatic enzymes in the plasma, the mortality rate may exceed 40%. Conventional treatment includes aggressive antibiotic therapy, fluid management, early enteral nutrition, and even surgical debridement. Recently, the powerful digestive proteases in the intestine have been identified in experimental sepsis and shock as initiators of the systemic inflammatory response (autodigestion hypothesis). Intraluminal blockade of proteases significantly suppresses the systemic inflammation and peripheral organ failure in experimental shock. But the hypothesis is untested in man. Gabexate mesilate, a synthetic compound with protease inhibitor but less lipase and amylase activity, significantly attenuates systemic inflammatory responses in experimental shock when delivered into the intestinal lumen to block the digestive proteases. Herein we have presented a case with continuous tube feeding into the digestive track with gabexate mesilate, which was followed by rapid reversal of septic indicators and shock symptoms. This case report received approval by our Human Ethics Committee and written consent of the patient.

CASE REPORT

A 58-year-old male heart transplant patient was regularly followed in the clinic for 4 years using cyclosporine, mycophenolate, and prednisolone therapy. The cyclosporine level was maintained at 150 to 200 mg/dL without evidence of rejection or infection. Before admission, he experienced a motorcycle accident with perineal trauma. The wound, which was self-managed by the patient, deteriorated after 1 week. He was hospitalized and immediately admitted to the intensive care unit. At presentation, his blood pressure was 80/40 mm Hg despite aggressive fluid management with 2 L of crystalloid and colloid over 5 hours and vasopressor therapy with dopamine (5 µg/kg/min). Emergent surgical debridement of the perineum was performed but his clinical condition did not improve. He was intubated and prescribed broad-spectrum antibiotics, including teichomycin, meropenem, and caspofungin. The blood chemistry values of amylase and lipase kept increasing (Fig 1). An X-ray of the abdomen showed a...
dilated small intestine with ileus. At the same time, a computed
tomography of the abdomen did not show edema in or fluid
accumulation over the pancreatic area. The diagnosis was
Fournier’s gangrene complicated by septic shock and multiple
organ failure. Due to persistent shock and worsening septic
markers, the patient received in addition a diverting colostomy
and intravenous total parental nutrition. Furthermore, the patient
underwent a second wide debridement. The wound culture was
positive for multiple drug-resistant *Pseudomonas aeruginosa*
and *Bacteroides thetaiotaomicron*.

Intravenous gabexate mesilate (3000 mg/d) was administered
due to the severe septic shock with elevated amylase and lipase
values as markers for presence of pancreatic enzymes. At the same
time, the patient stopped enteral feedings and underwent total
parental nutrition with a positive fluid balance of more than 1 L per
day. However, these therapies did not reduce plasma amylase and
lipase values over the next 12 hours; instead both values continued
to rise.

We then switched to “enteral gabexate mesilate infusion” into
the digestive tract by continuous feeding into the stomach via a
nasogastric tube using 3000 mg/d in 2000 mL of normal saline.
Within 2 days the blood pressure stabilized with minimal doses of
dopamine, the glucose levels were controlled with reduced doses of
subcutaneous insulin, and the patient’s level of conscience im-
proved. On the third day, the dose of gabexate mesilate was
reduced to 300 mg/d in a fluid volume of 2000 mL a level that was
maintained for 10 days before discharge from the intensive care
unit. The amylase, lipase, and white blood cell count decreased to
normal values (Fig 1) and his improved level of consciousness,
allowing us to remove the endotracheal tube within 6 days and to
start feeding within 2 weeks. The dopamine dose needed to maintain blood pressure was
decreased to less than 3 μg/kg/min, the ileus and intestinal
function improve, and he was discharged from the intensive
care unit after 2 weeks.

A single large dose of gabexate mesilate intraluminally
has been reported to decrease the severity of pancreatitis,
but not to reverse it. The oral form of gabexate mesilate

**DISCUSSION**

The mortality rate is high among patients with septic shock,
requiring aggressive antibiotic therapy, fluid management,
enteral nutrition, and even surgical debridement. But un-
fortunately, none of these therapies improve significantly
the mortality and morbidity. Experimental shock research
in animals has identified proteases, including trypsin, chy-
motrypsin, elastase, and matrix metalloproteinases, as ini-
tiators of the systemic inflammatory response. The “autodi-
gestion” hypothesis suggests that powerful digestive proteases
leak across the mucosal barrier, initiating a systemic inflam-
matory response with multiorgan failure. Intraluminal treat-
ment with a protease inhibitor ameliorates these complica-
tions in animals.

This critically ill patient on chronic immunosuppression
therapy developed septic shock and multiple organ failure
requiring wide surgical debridement, a diverting colostomy,
aggressive fluid management, and broad-spectrum antibiot-
ics. Intravenous gabexate mesilate was prescribed but
failed to improve his condition, an outcome consistent with
the failure of intravascular protease inhibitors in experi-
mental forms of shock since the achieved concentrations
are insufficient to block the concentrated, fully activated
digestive enzymes in the intestinal lumen.

In contrast, inhibition of digestive proteases directly in
the intestinal lumen reversed the indicators for shock.
Therefore we shifted the therapy to continuous enteral
feeding of gabexate mesilate. The patient’s clinical condi-
tion improved within days, as indicated by decreasing
values of amylase and lipase (Fig 1) and his improved level of
consciousness, allowing us to remove the endotracheal
tube within 6 days and to start feeding within 2 weeks. The
dopamine dose needed to maintain blood pressure was
decreased to less than 3 μg/kg/min, the ileus and intestinal
function improve, and he was discharged from the intensive
care unit after 2 weeks.

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**Fig 1.** (A) Time course of white blood cell (WBC) count and amylase and lipase activity before and during treatment. Values for all three
parameters decreased rapidly after continuous enteral gabexate mesilate feeding. The measurement units are: amylase (IU/mL); lipase
(U/mL) WBC: 10/L. (B) X-ray of abdomen on day 1 showed diffuse ileus and thickening of the intestinal wall. (C) X-ray of abdomen on day
16 showed improved ileus after continuous enteral gabexate mesilate treatment. (D) Computed tomography of abdomen without contrast
showed isodensity between pancreas and liver. This finding is not in support of a pancreatic inflammation.
(camostate), a synthetic compound with protease inhibitor activity, is used to attenuate protease activity in pancreatitis. Oral camostate can decrease pain, improve diabetic control and mitigate the severity of pancreatitis. We used continuous intraluminal protease inhibition to attenuate indices for sepsis and the systemic inflammatory response. Since gabexate mesilate may block thrombosis, we plan to decrease the dose in future cases and in clinical trials while maintaining its protective effects against digestive proteases. This case also provided evidence that while the intravascular infusion of gabexate mesilate may serve to protect against protease activity in the blood, the concentrations via the vascular pathway were insufficient to block the comparatively high intraluminal protease activity in the digestive track.

In conclusion, we have presented a case in which continuous feeding of a pancreatic protease inhibitor, gabexate mesilate, directly into the digestive track rapidly reversed indicators of a systemic inflammatory response and the sequelae of septic shock.

REFERENCES


