

Commentary

Acute pancreatitis: a possible role for activated protein C?

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See related research by Yamanel *et al.* in this issue [<http://ccforum.com/content/9/3/R184>]

Abstract

Acute pancreatitis results from a sequence of events that involve the systemic inflammatory response. Activated C has multiple anti-inflammatory activities and may attenuate the degree of pancreatic injury and systemic organ dysfunction when infused early in pancreatitis

Acute pancreatitis results from a sequence of pathologic events that involves the systemic inflammatory response [1,2]. The initial event is activation and retention of digestive enzymes in the acinar cells, with subsequent cellular injury. In addition, the acinar cells release inflammatory mediators, which leads to recruitment of neutrophils, formation of free radicals, and activation of the complement system. The neutrophils and macrophages generate additional cytokines, nitric oxide, platelet-activating factor (PAF), and other substances. The amplified inflammatory response exacerbates the pancreatic injury, causing evolution from an edematous to a necrotic pancreas. Spillage of the inflammatory mediators into the systemic circulation produces organ failure. The importance of the inflammatory cascade in this process is evidenced by the correlation of serum IL-6 with disease severity in acute pancreatitis [3].

Multiple experimental studies have examined the role of therapies directed at modulating the inflammatory response in acute pancreatitis. The hypothesis is that interventions, applied early in the course of pancreatitis, can attenuate the severity of pancreatic injury and the associated systemic organ dysfunction. Agents directed at tumor necrosis factor (TNF), IL-1, nuclear factor- κ B, inhibitors of lipid peroxidation, and PAF are among those that have been demonstrated to reduce the severity of pancreatic injury in experimental models [1]. The PAF antagonist lexipafant has also been studied in clinical pancreatitis. However, in a large multicenter trial [4] administration of lexipafant did not result in a significant decrease in mortality or in the severity of the pancreatitis.

Activated recombinant protein C (APC), a derivative of a naturally occurring anticoagulant, reduces mortality in severe sepsis [5]. In addition to its anticoagulant and profibrinolytic properties, APC appears to modulate the inflammatory response through multiple other mechanisms [6,7]. It has direct effects on neutrophil integrin expression and neutrophil-endothelial cell interactions. Inhibition of nuclear factor- κ B activation, TNF release, and induction of nitric oxide synthetase have also been demonstrated. In addition, APC also appears to have an antiapoptotic effect. These observations have led to the utilization of APC in other syndromes in which inflammation and neutrophil mediated injury play central roles, such as reperfusion, and spinal cord and radiation injury.

A study by Yamanel and coworkers [8], presented in this issue of *Critical Care*, examines the role played by APC in reducing pancreatic injury in a taurocholate induced model of acute pancreatitis. APC given 6 hours after the induction of pancreatitis significantly reduced acinar necrosis, tissue edema, fat necrosis, and inflammatory infiltration compared with controls. However, tissue hemorrhage scores were not different between groups. These changes were associated with a reduction in serum TNF, IL-6, and amylase levels.

These results suggest that APC may reduce the inflammatory process associated with pancreatitis. As is the case with severe sepsis, it is difficult to determine which mechanisms of action play the primary role in ameliorating tissue injury in this model. The observation that hemorrhage scores were not reduced, in concert with the other pathologic findings, is a matter of concern. The authors interpretation is that this finding suggests an 'intact coagulation system'. An alternative perspective is that, in the presence of decreases in all other parameters of histologic injury, the lack of a parallel change in the hemorrhage score indicates an increased bleeding risk associated with APC. The relative importance of this

complication is not clear, given the lower systemic cytokine and amylase levels in the APC treated animals. One element missing in the study is a histopathologic score at 6 hours before the administration of APC. Whether APC attenuates the progression from edematous pancreatitis to necrotizing pancreatitis, or whether it limits the severity of established necrotizing pancreatitis has important clinical implications. Indeed, one explanation for the therapeutic failure of the PAF antagonist lexipafant is that it might have been administered too late in the clinical course to be of benefit.

The development of a secondary infection in necrotic pancreatic tissue is an important complication that contributes to morbidity and mortality in acute pancreatitis [9]. Translocation of enteric bacteria from the intestine is postulated to play an important role in the development of this complication. In the study by Yamanel and coworkers [8], APC was also found to reduce significantly the incidence of culture positive mesenteric lymph nodes and pancreatic tissue. The authors suggested that this may be related to APC induced downregulation in inducible nitric oxide synthase activity. However, the role of nitric oxide in bacterial translocation in pancreatitis is controversial. Others have suggested that nitric oxide substrates may reduce bacterial translocation by preserving microvascular blood flow [10]. To the extent that this mechanism is important in maintaining the integrity of the intestinal barrier, the benefit observed with APC may have been related to its effects in reducing leukocyte-endothelial cell interactions, thereby improving the intestinal microcirculation [11].

The data from the study by Yamanel and coworkers [8] are preliminary and require confirmation in other models of pancreatitis. It would also seem important to determine whether the benefit of APC, if any, in experimental acute pancreatitis occurs before or after the development of acute necrotizing pancreatitis. As currently approved, whether in the USA or Europe, APC is utilized for established severe sepsis with complications. In contrast, the study presented in this issue, as well as much of the experimental work in this area, represents an effort to intervene early in pancreatitis in order to reduce the progression to severe necrotizing pancreatitis, with its attendant complications [1,12]. The concept of utilizing APC prophylactically in a clinical syndrome represents a new and intriguing application of this agent.

Competing interests

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