

Commentary

Drotrecogin alfa (recombinant human activated protein C) in severe acute pancreatitis

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Abstract

Introduction Current concepts of the pathophysiology of acute pancreatitis suggest that disease progression from acinar injury to systemic illness involves a complex interplay between cellular and soluble inflammatory mediators and endothelial beds. To date, there is no specific pharmacologic intervention for acute pancreatitis. Death from acute pancreatitis remains a major issue, and late deaths are often related to haemorrhage and are associated with unresolved intra-abdominal sepsis. Drotrecogin alfa, an analogue of endogenous protein C, has antithrombotic, anti-inflammatory and profibrinolytic properties, and it has been shown to reduce mortality in clinical sepsis. Modulation of the coagulation cascade, although probably essential to the mode of action of drotrecogin alfa, can lead to an increased risk of bleeding.

Objective The findings of the PROWESS trial have led to a more widespread use of drotrecogin alfa in sepsis and, critically, in sepsis-related conditions. The present article provides a concise summary of the interaction between the pathophysiology of acute pancreatitis and the modes of action of drotrecogin alfa, placing particular emphasis on the risks related to haemorrhage. Attention is further drawn to the reports of use of drotrecogin alfa in severe acute pancreatitis.

Conclusions Synthesis of current knowledge on the modes of action and the side-effect profiles of drotrecogin alfa into a practical management algorithm must accept that evidence in this field is changing rapidly. At present there is insufficient evidence to justify the use of drotrecogin alfa in the early stages of this disease. In the later stages, when the probability of infection is proportionately greater, it is probable that intensive care clinicians will turn to drotrecogin alfa, in particular, in the setting of recent-onset organ dysfunction in established severe acute pancreatitis. Although this can be justified by extrapolation of the evidence from the PROWESS trial, practical critical care management in this setting must not overlook the need to rule out infection of necrosis, and must further be cognisant of the specific risks of haemorrhage in patients with prolonged pancreatitis and pancreatic necrosis.

The early stages of severe acute pancreatitis are characterised by a profound systemic inflammatory response [1]. Current evidence is equivocal regarding the role of

infective agents at this stage of the disease process. Although there is increased intestinal permeability to macromolecules associated with a fall in endotoxin antibody in severe disease, use of the polymerase chain reaction fails to show early evidence of circulating bacterial genomic products [2].

In contrast, the later stages of severe acute pancreatitis are dominated by the sequelae of peri-pancreatic sepsis [3]. Although peri-pancreatic sepsis follows a similar course to other forms of intra-abdominal sepsis, a specific disease-related complication is the high risk of catastrophic intra-abdominal haemorrhage [3]. The pathophysiology of bleeding at this stage of the disease is multifactorial but may be related to the effects of chronic exposure to pancreatic juice in the lesser sac as a consequence of pancreatic ductal blow-out [4].

The search for treatments for severe sepsis has increasingly focused on the interplay between inflammation, microvascular coagulation and endothelial cell injury, and this has led to the development of drotrecogin alfa (recombinant human activated protein C) [5]. Drotrecogin alfa (Xigris; Eli Lilly, Indianapolis, IN, USA) is a 55 kDa glycoprotein analogue of endogenous protein C that is synthesised and secreted by genetically engineered human cells [5]. Endogenous protein C is a vitamin K-dependent glycoprotein synthesised by the liver. Under normal physiological conditions the protein C pathway plays an important role in the maintenance of haemostasis and the modulation of inflammation. Activation of protein C by thrombin-dependent endothelial binding inhibits thrombin generation and stimulates fibrinolysis [6]. In addition, activated protein C has anti-inflammatory properties related, in part, to inhibition of monocyte tumour necrosis factor alpha production and the modulation of E-selectin expression by endothelial cells [7]. The conversion of protein C to activated protein C is impaired during sepsis, and reduced

levels of markers of activated protein C correlate with increased morbidity in patients with sepsis [8]. It has been known for some time that similar changes in protein C activation occur in experimental acute pancreatitis [9].

In 2001, the PROWESS trial group reported the phase III randomised trial of drotrecogin alfa in 1690 patients with severe sepsis [10]. The principal outcome was an absolute reduction of 6.1% in the risk of death at 28 days [10]. In light of this evidence it was perhaps inevitable that drotrecogin alfa would be used more widely [11] in patients, including those with severe acute pancreatitis. A recent report describes the use of this drug in two patients with severe acute pancreatitis [12]. There was one death but the authors conclude that the cases indicate the efficacy of drotrecogin alfa in severe acute pancreatitis.

These reports highlight an acute dilemma in contemporary critical care practice: there is a dearth of specific treatment for severe acute pancreatitis, yet although drotrecogin alfa holds promise in sepsis, is it safe for use in severe acute pancreatitis? In the absence of specific clinical trial evidence, pragmatic answers can be found in the details of the PROWESS trial. Patients were included only if they had new-onset organ dysfunction (sepsis-induced dysfunction of at least one organ or system that lasted no longer than 24 hours) [10]. Although pancreatitis was a listed exclusion criterion for the PROWESS trial, 3.4% of patients receiving the drug had pancreatitis listed as a prior or pre-existing condition. It is highly relevant that the main cause of sepsis in patients in the PROWESS trial was of lung origin. Primary intra-abdominal sepsis was the second most frequent cause. A 'serious bleeding event' occurred in 30 patients (3.5%) receiving drotrecogin alfa as compared with 17 patients (2%) receiving placebo. This difference was not statistically significant ($P=0.06$). The PROWESS trial authors state that serious bleeding occurred primarily in patients with an identifiable predisposition to bleeding.

Synthesis of these findings into a practical management algorithm must accept that evidence in this field is changing rapidly. Recognising that patients with severe acute pancreatitis are currently being treated with drotrecogin alfa, however, a practical position for current management would be that, despite the experimental evidence of protein C activation in the early stage of experimental acute pancreatitis, there is insufficient evidence to justify the use of drotrecogin alfa in the early stages of this disease. In the later stages, when the probability of infection is proportionately greater, it is probable that intensive care clinicians will turn to drotrecogin alfa. In the setting of recent-onset organ dysfunction in established severe acute pancreatitis there is ample evidence that infection of pancreatic necrosis is a major source of deterioration, and the availability of new drugs must not blind clinicians to the need to search for, find and treat infected pancreatic necrosis [13]. This need is

made more imperative by the risk of bleeding in untreated peri-pancreatic sepsis.

In conclusion, drotrecogin alfa appears to represent a genuine advance in the treatment of human sepsis but, in the face of critical illness in severe acute pancreatitis, a vogue for the use of new medications must not replace the need to detect and treat infected pancreatic necrosis.

Competing interests

The author(s) declare that they have no competing interests.

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