CRITICAL CARE

COMMENTARY

Activated protein C in severe acute pancreatitis without sepsis? Not just yet …

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See related research by Pettila *et al.*, http://ccforum.com/content/14/4/R139/abstract

Abstract

Severe acute pancreatitis (SAP) is characterized by an unregulated systemic proinflammatory response secondary to activation of trypsin within the pancreatic tissue, resulting in multiple organ failure. This dysregulated inflammation leading to organ dysfunction also characterizes severe sepsis. Activated protein C (APC) has pleotropic effects on the immune, coagulation, inflammatory and apoptotic pathways, and has been postulated to benefit acute pancreatitis – although concerns of possible retroperitoneal bleeding remain. Currently, experimental studies and subgroup data on patients with pancreatitis from a randomized controlled trial of APC in severe sepsis form the literature on the possible role of APC in SAP. We review the first randomized controlled trial of APC in acute pancreatitis published in the present issue of *Critical Care*.

In the present issue of *Critical Care*, Pettila and colleagues report the first single-centred pilot randomized controlled trial of activated protein C (APC) in alcohol-induced acute pancreatitis of moderate severity but without infection [1]. After screening 215 patients, 32 patients satisfied the trial inclusion criteria and were randomized to either placebo or APC at 24 µg/kg/hour for 96 hours, in addition to standard therapy for acute pancreatitis. The study – powered to evaluate the effect of APC on the change in organ dysfunction, measured using the Sequential Organ Failure Assessment score as the primary outcome – failed to show any benefit.

In acute pancreatitis, severity is defined by the occurrence of organ failure and/or peri-pancreatic complications. Severe acute pancreatitis (SAP) is characterized by the presence of an overwhelming inflammatory response,

with unregulated activation of the coagulation system. Evaluation of the coagulation and the endogenous protein C/antithrombin III (AT III) system shows that nonsurvivors in SAP have significantly lower levels of protein C and AT III activity, and higher levels of D-dimer and plasminogen activator inhibitor-1, than survivors [2]. These changes mirror the patterns seen in severe bacterial sepsis that suggest exhaustion of fibrinolysis and coagulation inhibitors, thereby identifying a possible role for APC in SAP independent of the need to diagnose severe sepsis. Prior to the study by Pettila and colleagues [1], the literature was limited to animal studies [3,4] and to subgroup data from the PROWESS trial of 62 patients with acute pancreatitis and severe sepsis, where there was a trend to reduced mortality in those treated with APC (24% vs. 15%) [5]. The Consensus Guidelines thus recommended that careful consideration is given to APC therapy in those patients with SAP and infection, given the theoretical but unproven concern of retroperitoneal haemorrhage [5].

SAP is a devastating disease with an attributable mortality of around 30%, and thus interventional trials are required to find a potential therapy to improve outcome. Although commendable, this pilot trial of APC in pancreatitis must be interpreted with caution. As the authors point out, the study is underpowered to detect any meaningful difference in the primary outcome – change in the Sequential Organ Failure Assessment score – as a surrogate for APC effect. The authors also report no difference in bleeding complications, yet serious bleeding is actually a relatively infrequent event in patients treated with APC. In a meta-analysis of 10,679 APC-treated patients, the incidence of serious bleeding was 3.3% [6]. This equates to approximately one serious bleeding event per 30 patients; consequently, in a study involving only 16 APC-treated patients it is difficult to draw any clinically relevant conclusions (good or bad) with respect to bleeding.

The mortality benefit with APC is best shown in patients with severe sepsis and high risk of death; for example, patients with multiple organ dysfunction, patients with Acute Physiology and Chronic Health Evaluation (APACHE) II score ≥25, or those in shock [7]. There has

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always been debate regarding benefit in the patients at low risk of death, such as those in the lowest quartile of the PROWESS trial (that is, APACHE II score <17). The severity of illness and risk of death due to acute pancreatitis in this pilot trial was low (mean age of 47, mean APACHE II score of 14 and zero mortality in the control arm). Moreover, 34% of the patients never required invasive ventilation and 37% never developed shock requiring a vasopressor. The population studied is thus likely to be confounding the results. Indeed, for subsequent trials with APC the inclusion criteria have all focused on ensuring high severity of illness, including the important ongoing PROWESS-SHOCK trial [8,9].

Identifying individual patients who are likely to benefit the most and to suffer the least morbidity from an intervention is a challenge, and there is an increasing role for biomarkers to assist in this endeavour. In the context of APC, serial measurements of protein C may be the best biomarker in establishing those most at risk of poor outcome in severe sepsis, may highlight those patients most likely to benefit from APC, and also may prove useful in monitoring therapy [10]. As protein C deficiency has been demonstrated in experimental early SAP, this trial might have been more relevant had it measured protein C as a biomarker. In addition, the observed low mortality in the study highlights the importance in study design of selecting a population who are genuinely at high risk of death and are potential ideal candidates for what is an expensive and debated therapy [2,11].

This pilot study is underpowered to contribute significantly to the baseline data necessary to inform the design of a future interventional trial assessing APC as a potential therapy in SAP. If further trials with APC are undertaken in this disease, it is essential they have the scope and ability to capture a genuinely high-risk population and provide the intervention in a timely manner. Consideration should be given to selecting patients at highest risk of progressive organ dysfunction defined by at least moderate protein C deficiency.

Abbreviations
APACHE, Acute Physiology and Chronic Health Evaluation; APC, activated protein C; SAP, severe acute pancreatitis.

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