Commentary

Anticoagulant therapy in acute lung injury: a useful tool without proper operating instruction?

Sebastian Rehberg, Perenlei Enkhbaatar and Daniel L Traber

Department of Anesthesiology, The University of Texas Medical Branch, 301 University Blvd, 77555 Galveston, TX, USA

Corresponding author: Sebastian Rehberg, serehber@utmb.edu

Published: 22 September 2008
This article is online at http://ccforum.com/content/12/5/179

Critical Care 2008, **12:**179 (doi:10.1186/cc7002)

See related research by Waerhaug *et al*., http://ccforum.com/content/12/4/R104

Abstract

Activation of the coagulation cascade resulting in alveolar fibrin deposition is recognized as a hallmark of acute lung injury (ALI). Anticoagulant treatment with recombinant human activated protein C (rhAPC) appears promising, because - like in sepsis - there is a deficiency of protein C in ALI, which is correlated with poor outcome in both syndromes. Recently in *Critical Care*, Waerhaug and colleagues confirmed the beneficial effects of rhAPC on pulmonary function in ovine endotoxin-induced ALI. Notably, the authors reported no differences in hemorrhage in histologic analyses between rhAPC-treated and untreated animals. However, a recently reported randomized, placebo-controlled, multicenter trial in ALI patients without severe sepsis failed to identify any differences in the number of ventilator-free days or 60 day-mortality between the rhAPC and placebo group. In addition to (or perhaps because of) the complex pathogenesis, the discrepancy between clinical and experimental results in ALI is another common feature with sepsis. The future challenge will be to transfer our theoretical knowledge adequately into daily clinical practice. Anticoagulant therapy might be a useful tool in the treatment of ALI; however the proper operating instruction remains to be defined.

Activation of the coagulation cascade resulting in alveolar fibrin deposition is recognized as a hallmark of acute lung injury (ALI) [1] and acute respiratory distress syndrome (ARDS) [2]. Consequently, anticoagulant and fibrinolytic therapies in ALI with various compounds, such as heparin, tissue factor pathway inhibitor, antithrombin, activated protein C, recombinant soluble thrombomodulin, urokinase plasminogen activator, or tissue plasminogen activator, have been investigated in recent years. Activated protein C treatment appears to be very promising, because - like in sepsis - there is a deficiency of protein C in ALI/ARDS, which is correlated with poor outcome in both syndromes [3,4]. Although recombinant human activated protein C (rhAPC) therapy in sepsis is still controversial [4,5], experimental data for the use of rhAPC in ALI are encouraging [6-8].

Recently in *Critical Care*, Waerhaug and colleagues [1] reported the results of a timely and carefully conducted experiment designed to elucidate the effects of an intravenous continuous infusion of 24 μg/kg per hour rhAPC in ovine endotoxin-induced ALI. The rhAPC treatment was started 4 hours after the initiation of the lipopolysaccharide infusion. In addition, a sham group, a control group with the injury only, and a group only receiving rhAPC infusion were examined. In agreement with previous studies [6-8], the authors demonstrated improvements in oxygenation and pulmonary hemodynamic and volumetric variables, as well as anti-inflammatory properties of rhAPC in treated animals as compared with control animals.

Interestingly, rhAPC prevented the translocation of protein kinase C α and ε in the cytosol fraction of lung tissue. In addition, reduced edema formation and decreased pulmonary vascular permeability index were noted in the rhAPC group as compared with control animals. Based on these two findings, the authors hypothesized that rhAPC was potentially responsible for preservation of vascular integrity. When interpreting these findings, the reader should be aware that lung edema formation was not prevented by rhAPC in our model of smoke inhalation and *Pseudomonas aeruginosa* induced pneumonia [6]. These contrary results might be accounted for by the difference in the severity of ALI. Although the authors stated that two animals died because of endotoxin-induced ALI, the extent of oxygenation impairment did not reach the ALI defining ratio of arterial partial oxygen pressure to inspired oxygen fraction (≤300). In addition, an endotoxin-induced sepsis does not necessarily mimic the situation in humans as adequately as models using live bacteria [9].

Histologic analyses revealed no differences in hemorrhage in lung tissue between rhAPC-treated or control animals in the

ALI = acute lung injury; ARDS = acute respiratory distress syndrome; rhAPC = recombinant human activated protein C.

study by Waerhaug and colleagues [1]. In accordance with these results, a randomized multicenter trial in ALI patients also did not identify an increased frequency of bleeding events in the rhAPC group [10]. However, greater incidences of bleeding complications in rhAPC-treated patients as compared with placebo were described in several sepsis trials [4,11,12]. Against this background, further research is warranted to verify the absence of additional bleeding events during rhAPC therapy in ALI.

Contrary to the findings of Waerhaug and colleagues [1], a recently published randomized placebo-controlled, multicenter trial in ALI patients without severe sepsis and an Acute Physiology and Chronic Health Evaluation II score below 25 [10] failed to show any differences in the number of ventilator-free days or 60-day mortality between the rhAPC and placebo group. The essential question is, why do promising treatment strategies tested in experimental models often fail in randomized, clinical trials? Is the inefficiency of the investigated drug really always the cause? In addition to (or perhaps because of) the complex pathogenesis, this problem in ALI is another feature in common with sepsis [9,13]. Many methodologic differences between experimental and large clinical trials must be taken into consideration. On the one hand there are well defined, standardized injuries, strictly scheduled protocols in a homogenous setting with young, healthy animals, and an observation period rarely exceeding 24 hours. On the other hand, clinical studies are performed simultaneously with daily patient care; they include the broad spectrum of injuries that cause ALI in predominantly elderly patients with secondary complications in different hospitals, and they investigate long-term variables such as ventilator-free days or 90-day mortality. Against this background, the 'failure' of a drug in large clinical trials should not be defined as an end-point.

We should try to develop more translational studies instead, probably resulting in a decreased number of included patients but hopefully in a more successful therapy. Further research is warranted to define the conditions in which the individual ALI patient might benefit from rhAPC. Two examples might emphasize this postulation. First, it appears to be beneficial to initiate rhAPC treatment early in inhalation injury in order to prevent obstructive cast formation [6]. However, in sepsis or pneumonia, prophylactic or immediate rhAPC infusion was shown to be harmful [14] because procoagulatory activity may limit the inflammatory process in the early stages of ALI. Second, the frequency of bleeding complications might be decreased by inhalational administration of rhAPC. This local treatment was shown to reduce coagulation, inflammation, and vascular leakage in endotoxin-induced ALI in mice [15].

In summary, experimental studies on this topic - together with the current work of Waerhaug and colleagues [1] - provide evidence for the effectiveness of anticoagulant therapy in ALI. The future challenge will be to transfer our theoretical knowledge adequately into daily clinical practice. Anticoagulant therapy might be a useful tool in the treatment of ALI, but the proper operating instruction remains to be defined.

Competing interests

The authors declare that they have no competing interests.

References

1. Waerhaug K, Kuklin VN, Kirov MY, Sovershaev MA, Langbakk B, Ingebretsen OC, Ytrehus K, Bjertnaes LJ: **Recombinant human activated protein C attenuates endotoxin-induced lung injury in awake sheep.** *Crit Care* 2008, **12:**R104.
2. Schultz MJ, Haitsma JJ, Zhang H, Slutsky AS: **Pulmonary coagulopathy as a new target in therapeutic studies of acute lung injury or pneumonia: a review.** *Crit Care Med* 2006, **34:**871-877.
3. Network TA: **Ventilation with lower tidal volumes as compared with traditional tidal volumes for acute lung injury and the acute respiratory distress syndrome. The Acute Respiratory Distress Syndrome Network.** *N Engl J Med* 2000, **342:**1301-1308.
4. Bernard GR, Vincent JL, Laterre PF, LaRosa SP, Dhainaut JF, Lopez-Rodriguez A, Steingrub JS, Garber GE, Helterbrand JD, Ely EW, Fisher CJ Jr; Recombinant human protein C Worldwide Evaluation in Severe Sepsis (PROWESS) study group: **Efficacy and safety of recombinant human activated protein C for severe sepsis.** *N Engl J Med* 2001, **344:**699-709.
5. Marti-Carvajal A, Salanti G, Cardona AF: **Human recombinant activated protein C for severe sepsis.** *Cochrane Database Syst Rev* 2008, **1:**CD004388.
6. Maybauer MO, Maybauer DM, Fraser JF, Traber LD, Westphal M, Enkhbaatar P, Cox RA, Huda R, Hawkins HK, Morita N, Murakami K, Mizutani A, Herndon DN, Traber DL: **Recombinant human activated protein C improves pulmonary function in ovine acute lung injury resulting from smoke inhalation and sepsis.** *Crit Care Med* 2006, **34:**2432-2438.
7. Murakami K, Okajima K, Uchiba M, Johno M, Nakagaki T, Okabe H, Takatsuki K: **Activated protein C prevents LPS-induced pulmonary vascular injury by inhibiting cytokine production.** *Am J Physiol* 1997, **272:**L197-L202.
8. Yoshikawa A, Kaido T, Seto S, Katsuura Y, Imamura M: **Activated protein C prevents multiple organ injury following extensive hepatectomy in cirrhotic rats.** *J Hepatol* 2000, **33:**953-960.
9. Esmon CT: **Why do animal models (sometimes) fail to mimic human sepsis?** *Crit Care Med* 2004, **32(suppl):**S219-S222.
10. Liu KD, Levitt J, Zhuo H, Kallet RH, Brady S, Steingrub J, Tidswell M, Siegel MD, Soto G, Peterson MW, Chesnutt MS, Phillips C, Weinacker A, Thompson BT, Eisner MD, Matthay MA: **Randomized clinical trial of activated protein C for the treatment of acute lung injury.** *Am J Respir Crit Care Med* 2008, **178:**618-623.
11. Vincent JL, Bernard GR, Beale R, Doig C, Putensen C, Dhainaut JF, Artigas A, Fumagalli R, Macias W, Wright T, Wong K, Sundin DP, Turlo MA, Janes J: **Drotrecogin alfa (activated) treatment in severe sepsis from the global open-label trial ENHANCE: further evidence for survival and safety and implications for early treatment.** *Crit Care Med* 2005, **33:**2266-2277.
12. Abraham E, Laterre PF, Garg R, Levy H, Talwar D, Trzaskoma BL, François B, Guy JS, Brückmann M, Rea-Neto A, Rossaint R, Perrotin D, Sablotzki A, Arkins N, Utterback BG, Macias WL; Administration of Drotrecogin Alfa (Activated) in Early Stage Severe Sepsis (ADDRESS) Study Group: **Drotrecogin alfa (activated) for adults with severe sepsis and a low risk of death.** *N Engl J Med* 2005, **353:**1332-1341.
13. Westphal M, Ertmer C: **Dear sepsis trials, why do you like playing tricks on us?** *Curr Opin Anaesthesiol* 2008, **21:**95-97.
14. Robriquet L, Collet F, Tournoys A, Prangere T, Neviere R, Fourrier F, Guery BP: **Intravenous administration of activated protein C in *Pseudomonas*-induced lung injury: impact on lung fluid balance and the inflammatory response.** *Respir Res* 2006, **7:**41.

15. Slofstra SH, Groot AP, Maris NA, Reitsma PH, Cate HT, Spek CA: **Inhalation of activated protein C inhibits endotoxin-induced pulmonary inflammation in mice independent of neutrophil recruitment.** *Br J Pharmacol* 2006, **149:**740-746.