Should we be using activated protein C to treat severe sepsis?

Sepsis and septic shock are common syndromes occurring in the intensive care unit and are associated with a high mortality. Levels of endogenous activated protein C are reduced in sepsis and linked with poor outcome. This led to the development of recombinant human activated protein C (rhAPC, drotrecogin alfa (activated), Xigris) for the treatment of patients with severe sepsis. Its use in this condition has been recommended by the National Institute for Clinical Excellence (NICE), and the Surviving Sepsis Campaign guidelines (Dellinger et al, 2008) suggest that adult patients with sepsis-induced organ dysfunction associated with a clinical assessment of high risk of death, most of whom will have an APACHE II score ≥25 or multiple organ failure, receive this therapy.

However, there is ongoing debate regarding the use of rhAPC and uptake figures from NICE now show a reduction in the use of rhAPC. Is this reduced enthusiasm justified?

rhAPC should be given in severe sepsis

PROWESS (n=1690) was a phase III multicentre randomized controlled trial investigating the role of rhAPC in adult patients with severe sepsis (Bernard et al, 2001). Patients were randomized to an infusion of rhAPC over 96 hours or placebo. This demonstrated a 19.4% relative reduction and a 6.1% absolute reduction in 28-day mortality with rhAPC (number needed to treat = 16).

To obtain additional efficacy and safety data a single-arm open-label study known as ENHANCE (n=2378) was performed (Vincent et al, 2005). Entry criteria were similar to PROWESS and the trial showed a similar mortality rate to PROWESS at 28 days (25.3% *vs* 24.7%), providing supportive evidence for the use of rhAPC.

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rhAPC should not be given in severe sepsis

The mortality benefit reported in PROWESS has not been replicated in all patient groups. The ADDRESS trial (n=2613) was a randomized controlled trial investigating the role of rhAPC in patients with severe sepsis and a low risk of death (APACHE II score <25 or single organ failure) (Abraham et al, 2005). This failed to show a mortality benefit but serious bleeding occurred in more patients in the rhAPC group than with placebo during both the infusion (2.4% *vs* 1.2%) and the 28-day study period (3.9% *vs* 2.2%). In addition, surveys of clinical use of rhAPC have demonstrated higher rates of serious bleeding and mortality than those published in trial data. A further randomized controlled trial in paediatric patients has also failed to demonstrate survival benefit.

Over the last few years there have been questions raised about the efficacy of rhAPC, partly because of various aspects of the conduct of the PROWESS trial. Following the first interim analysis (which did not demonstrate a difference between groups) there were a number of important changes to the trial. An amendment was accepted enabling trial coordinators to exclude patients not expected to benefit from rhAPC. Also, following this amendment the master cell bank for drug production was changed. By the second interim analysis at 1690 patients a significant difference existed.

Blinding also proved problematic as rhAPC foamed when perturbed while the placebo (0.9% saline) did not. The placebo was changed to 0.1% albumin but this solution was not permitted in all centres. At this stage there was a change in do not resuscitate rates; these fell from 16% to 9% in the rhAPC group but with placebo remained at 18%. Additionally, 20 trial sites were removed and 45 sites added; dropped sites tended towards poor drug effect whereas added sites were more supportive of useful drug effect. Although in PROWESS there was a significant difference in 28-day mortality almost all of the survivors remained in hospital. When 90-day survival rates from this study were published there was no significant difference in survival between the groups. Another concern is the unvalidated use of APACHE II scores to determine treatment use.

Conclusions

There is a great deal of controversy over the use of rhAPC in the treatment of severe sepsis. A systematic review by the Cochrane collaboration has concluded that there is insufficient evidence to support its use and that there is an increased risk of bleeding (Martí-Carvajal et al, 2008). There is sufficient equipoise among the critical care community that a second randomized controlled trial called the PROWESS Shock trial is now underway which may define more precisely the role of rhAPC in this complex condition. **BJHM**

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Anaesthetic and critical care dilemmas are coordinated by Dr John Orr and Dr Annie Hunningher, Research Fellows at the Centre for Anaesthesia, UCL, London Ideas for future dilemmas can be sent to Rebecca Linssen bjhm@markallengroup.com